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Probing the Decisional Brain with rTMS and tDCS

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NONINVASIVE BRAIN STIMULATION

Probing brain function and its relation with behavior is one of the most intriguing challenges of our era. Until about 25 years ago the most reliable way to investigate human brain function via its altered states was limited to occurrences of lesions, intra-operatory stimulation, neurosurgical resections, and congenital malformations. In other words, it was not possible to independently manipulate the state of healthy brains in a targeted, reversible, and noninvasive manner as it is today. In the past quasi-experiments (i.e., experiments in which the independent variable had been manipulated by nature itself or based on primarily clinical considerations) were the gold standard. It has now become possible, instead, to experimentally modulate the state of neural circuits in the healthy human brain for basic research purposes.

With noninvasive brain stimulation the healthy brain is not structurally disrupted and its function is modulated only locally and for a limited amount of time. This new experimental approach, made possible by recent technical developments, can provide more accurate information about the intact system, upon which theoretical models of mental processes are based. It allows causal links to be drawn between neural states and behavior, where techniques such as functional magnetic resonance imaging (fMRI), event-related potentials (ERPs), and magnetoencephalography (MEG) can only report co-variations between brain activity and behavior and cannot tell whether a given neural substrate is necessary or not for a specific behavior (Walsh & Cowey, 2000). With noninvasive brain stimulation, the same participants – or a group of participants from the very same sample as the experimental participants – can serve as their own control. Control and experimental measures can be made within minutes and in the same session in within-subject designs. Functional reorganization, compensatory changes, and deficit attenuation do not have time to settle because the alteration in brain function is relatively short-lived (unless stimulation is regularly performed for rehabilitation or therapeutic purposes), thus this method is completely reversible and safe (Rossi, Hallett, Rossini, Pascual-Leone, & the "Safety of TMS Consensus Group", 2009). Moreover, given the relatively weak (and not necessarily disruptive) impact of noninvasive stimulation on cognitive resources, there is no need to create ad hoc, more affordable versions of already existing experimental protocols.

The use of electricity to alter neural function has a long history, and noninvasive stimulation with electrodes applied on the surface of the scalp has remained the main stimulation device in medical and experimental settings for centuries, in spite of being associated with painful sensations. However, the discovery of the principle of electromagnetic induction by Faraday in the 19th century paved the way to the advent of a new noninvasive brain stimulation technique (Barker, Freeston, Jalinous, Merton, & Morton, 1985). The principle that a changing magnetic field can induce an electric current in a neighbor electric means is indeed at the basis of transcranial magnetic stimulation (TMS), where a stimulation coil serves as an electromagnet that generates a rapidly changing magnetic field. When the coil is placed on the scalp and the magnetic field is directed to the brain, an electric current is induced in the underlying neural tissues with reasonable spatial (about 1–2 cm^2, varying with coil/brain geometry and stimulation parameters) and temporal resolution (in the order of a few tens of milliseconds).

TMS is thought to actively initiate action potentials in neurons and/or alter their level of excitability during and after stimulation, although its precise mechanisms of action are still far from clear: see Wagner, Rushmore, Eden, and Valero-Cabre (2009) for hypotheses on the mechanisms of action of TMS, and Miniussi, Ruzzoli, and Walsh (2010), Rusconi and Bestmann (2009), Siebner, Hartwigsen, Kassuba, and Rothwell (2009), and Ziemann (2010) for more general discussions on the interpretation of TMS effects in neurocognitive studies. A prolonged slow sequence of pulses (e.g., 1 Hz repetitive transcranial magnetic stimulation (rTMS) over an area for 10 min) produces modification in cortex excitability that can last for a few minutes after stimulation. A fast sequence of pulses (e.g., 10 Hz rTMS over an area for 500 ms) produces a transient modification supposedly locked in time with the train of pulses (Robertson, Théoret, & Pascual-Leone, 2003). The more recent theta-burst protocol, with triple-pulse stimulation at 50 Hz delivered every 200 ms (i.e., in the theta band, 5 Hz) for less than 1 min, has both rapidity and long-term efficacy (e.g., Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). rTMS can be applied online (i.e., during task performance) or offline (i.e., beforehand). The advantage of the offline approach compared to the online approach is that the participant can perform a task without any extraneous additional sensation or discomfort produced by active stimulation, and the difference between active and sham stimulation is less obvious to the participant. Its disadvantage consists of the necessity for resting periods, to wash out the effects of stimulation at any one site, thus lengthening experimental sessions. Moreover, temporal specificity is lost, since any kind of effect cannot be directly related to specific time windows during task execution, a drawback it shares with transcranial direct current stimulation (tDCS).

tDCS is a technique for modulating cortical excitability, which involves the application of two surface electrodes: an anode and a cathode. A weak (e.g., 1 mA or 2 mA) direct current is applied for up to 20 min between moistened sponge electrodes (usually having a surface of 35 cm^2) placed on the head. The current flows from the anode to the cathode, leading to increases or decreases of cortical excitability dependent on the direction and intensity of the current for up to 1 h post-stimulation (Miranda, Lomarev, & Hallett, 2006; Nitsche & Paulus, 2001). Typically, anodal tDCS exerts an excitatory effect on the underlying cerebral cortex via subthreshold depolarization of neurons, whereas cathodal stimulation has a hyperpolarizing effect. In general it can be conceptualized as a method to change the likelihood that an incoming action potential will result in post-synaptic firing in the areas underneath electrodes (Nitsche et al., 2003). tDCS produces a tingling sensation under the electrodes that is most noticeable at the beginning of a session; terminating the current after 30 s, for example, may thus provide a very desirable sham condition. Its limited temporal and spatial resolution makes it unsuitable for exploring fine neurophysiological mechanisms or dissecting mental processes (Wassermann, 2008). However, it is safe, inexpensive, wearable, can be compared to a sham condition that subjects cannot usually distinguish from real stimulation, and has already provided useful evidence in the neuroscientific study of both single-subject decision making and simultaneous social interactions with large experimental groups (see below). Electrical stimulation is now undergoing renewed interest due to technical improvements, which have enormously reduced painful sensations to the scalp, and the widespread acceptance of TMS as a research and potential clinical tool.

How to Do It

Selecting stimulation parameters (intensity, frequency, and duration) and a paradigm is a difficult and often arbitrary decision (for discussions of related issues, see: Paulus, 2003; Wasserman, Epstein, Ziemann, Walsh, Paus, & Lisanby, 2008). Beyond the physical parameters, which require expert guidance, one of the most important decisions an experimenter takes and a reader needs to be aware of is the choice of control conditions. While many control conditions are intuitive, such as the choice of an alternative stimulation area, one concept the reader may not be familiar with is one of "sham" stimulation. The stimulating procedure is associated with a number of sensory perceptions that can nonspecifically interfere with task performance. For instance, with TMS, the discharging coil produces a click sound that may induce arousal, thereby modulating task performance, irrespective of the exact demands of the experimental design (i.e., via intersensory facilitation). Sham rTMS stimulation is generally carried out by tilting the coil away from the scalp (Sandrini, Umiltà, & Rusconi, under review), so that the sound and the scalp contact are roughly similar to the active stimulation but the magnetic field does not reach the cortical neurons, cutaneous receptors, or superficial muscles. Sham-coils are also commercially available. They still produce the same sound during stimulation but no magnetic field is generated, so they can rest tangential to the scalp surface exactly as they are during active stimulation.

Safety Guidelines

Methodological issues cannot be entirely separated from safety and ethical considerations. The last decade has seen a rapid increase in the use of TMS to study cognitive functions: the brain–behavior relationship (see Sandrini et al., under review, for a synthesis). Transient side-effects of TMS and rTMS may include headache, neck ache, and mild discomfort, but they are secondary effects not directly related to the cortical stimulation itself, which instead may directly induce seizures. Based on the available empirical data the use of TMS and rTMS is safe, with concern only for stimulation protocols outside currently available safety guidelines. Considerations regarding the following main points should be kept in mind when designing a TMS or rTMS study (Rossi et al., 2009):

1. Research application must to be governed by three fundamental ethical and legal requirements: informed consent, risk–benefit ratio, and equal distribution of the burdens and benefits of research.
2. Based on their demands for protection of the subjects and expected benefits, studies with normal subjects are classified as providing indirect benefit and at low risk.
3. As for protocol safety, any "novel paradigm" (i.e., that is not a conventional method of high- or low-frequency rTMS performed with a flat butterfly coil and biphasic stimulation) or TMS applied on more than a single brain region, or any conventional high-frequency protocol with parameters (intensity, frequency, train length, or intertrial interval) exceeding the safety limits (see tables 4–6 in Rossi et al., 2009), will put the experimenter in a condition of increased or uncertain risk of inducing epileptic seizures.
4. It is a requirement to know where TMS should be done, who should do the TMS, and how to manage emergencies (syncope and seizures) (Rossi et al., 2009).
5. TMS candidates should undergo previous medical screening via a standard questionnaire.
6. Additional safety issues should be considered when performing TMS in the MRI area and/or in the MRI scanner.

The same general rules apply for tDCS, although much less has been written and published about its safety aspect. Very few reports found injuries (i.e., acute skin irritation under the sponges) and the technique is considered safe as long as one sticks to the parameters described in the literature. As for cognitive after-effects, to date reports of tDCS modulation have generally indicated only transient improvements or impairments, if any change at all (Bikson, Datta, & Elwassif, 2009).

NONINVASIVE BRAIN STIMULATION IN ECONOMIC DECISION MAKING: EMPIRICAL REPORTS

Decision making is a complex mental function recruiting a distributed cortico-subcortical network (e.g., Ernst & Paulus, 2005; Mobbs, Lau, Jones, & Frith, 2007). An important node in this network is the dorsolateral prefrontal cortex (DLPFC). We will summarize below the noninvasive stimulation studies that were conducted with a focus on the DLPFC and within a neuroeconomics perspective (see Table 9.1). By and large this is an overselective review, its purpose being to provide a sample of how noninvasive brain stimulation can be used in a decision making context. It does not therefore cover all of the available literature on decision making that focuses on different tasks and targets different brain areas: see, for example, Bestmann et al. (2008) for motor response preparation, Müri and Nyffeler (2008) for eye movements, and Jahanshahi, Profice, Brown, Ridding,

TABLE 9.1 Short summary table of the studies discussed in this chapter.

Study	*Method*	*Task*	*Sites*	*Main results*
Van't Wout et al. (2005)	6 Hz rTMS (25% max stimulator output) for 5 min followed by 1 Hz rTMS (45% max stimulator output) for 12 min	**Ultimatum Game** (offline)	F4 (right DLPFC)	Compared to sham, right DLPFC slows down rejection times to unfair offers + tendency to accept more unfair offers
Knoch et al. (2006a)	1 Hz rTMS (100% individual resting motor threshold) for 15 min	**Risk Task** (offline)	Left/right DLPFC	Compared to sham and left DLPFC stimulation, subjects receiving right DLPFC stimulation select the high-risk option more often
Knoch et al. (2006b)	1 Hz rTMS (100% individual resting motor threshold) for 15 min	**Ultimatum Game** (offline)	Left/right DLPFC	Compared to sham and left DLPFC stimulation, subjects receiving right DLPFC stimulation accept the unfair offer more often and faster, whereas fairness judgments remain unaffected
Knoch et al. (2008)	Cathodal tDCS	**Ultimatum Game** (social setting)	Right PFC	Fair behavior is reduced when suppressing right PFC activity
Fecteau et al. (2007a)	Anodal/cathodal bilateral tDCS	**Risk Task**	F3–F4 (left/right DLPFC)	The right anodal/left cathodal group showed more safe-prospect choices, responded faster, and earned more
Fecteau et al. (2007b)	Anodal/cathodal bilateral tDCS; anodal unilateral tDCS	**Balloon Analog Risk Task**	F3–F4 (left/right DLPFC)	Less pumps with bilateral stimulation; no risk-taking increase with time in both uni- and bilateral stimulation compared to sham; no effects in the Stroop task

Dirnberger, and Rothwell (1998) and Knoch, Brugger, and Regard (2005) for random number generation.

The DLPFC is a fundamental portion of the PFC commonly considered to be involved in cognitive control and inhibition of impulsive responses (Koechlin, Ody, & Kouneiher, 2003; Miller & Cohen, 2001). Thus, it could be expected to play an extremely important role in decision making, particularly when there is a conflict between emotional and rational motives (which, in the present context, coincide with economic self-interest), such as when a subject needs to decide between accepting or rejecting an unfair offer in the Ultimatum Game (Guth, Schmittberger, & Schwarze, 1982).

The Ultimatum Game[1] is about splitting a sum of money, where a "proposer" offers a share of the sum given to him to a "responder" who can accept or refuse the offer. If the offer is refused, both players leave empty-handed. This and other such games have been used to highlight the fact that humans do not always act as rational decision makers striving to maximize their gains. Indeed, in the Ultimatum Game, an offer that is judged unfair is generally rejected, even though doing so is financially disadvantageous (since even a small share is better than nothing; Fehr & Schmidt, 1999).

Models based on social preferences integrating the role of emotions propose to explain the evidence for fairness, trust, and reciprocity in social interactions. Cooperative behaviour occurs in all human societies (even though there are variations in threshold settings between fair and unfair in different cultures), but it is much less frequently observed in other species, from invertebrates up to and including nonhuman primates. The question thus arises whether possessing a specific cognitive ability or set of abilities is a prerequisite for cooperation and reciprocity to emerge in a social group. Describing the features of the human cognitive apparatus that make cooperation and reciprocity possible, and identifying the brain structures and processes that are responsible for such behaviour, are the main objectives of the emerging fields of neuroeconomics (Glimcher & Rustichini, 2004). Neuroscientists and economists have recently begun to study jointly how strategic thinking and emotions related to reward, self-interest, or fairness regulate human individual and social behaviour.

An increasing amount of research in neuroscience has implemented games and a game theoretical approach in designing behavioral tasks. Although game theory was initially developed as a branch of mathematics, it can now be considered a social science aimed at the understanding of decision makers' behavior in social contexts. The theory considers any social interaction involving two or more individuals as a game. It studies the series of actions that players can take in different classes of games and suggests solutions by examining the properties of such games. Games can describe any kind of interactive situations, from the simplest to very complex interactions between genes, people, firms, nations, etc; and game theory can provide analytical solutions to how players should play in games when given precise assumptions about their rationality. Game theory, a highly influential view in economics, states that individuals will strive to preserve the best possible outcome given the external constraints and the behaviour of other individuals (Von Neuman & Morgenstern, 1944). This theory can predict choices made in various situations involving strategic thinking or competitive interactions among individuals.

Studying cooperation and reciprocity is to a large extent about studying the mechanism for enforcing or reinforcing pro-social behaviour, which includes both positive (reward of pro-social behavior) and negative (punishment of social norms violations) drives. In social settings, violating the norm affects members of a group in terms of status, reputation, and exclusion. Punishment of "free-riders" in a society where cooperative behavior is expected is believed to be the main way through which norms are maintained, since the fear of punishment can deter selfish behaviour. As shown in the Ultimatum Game, punishment is costly and is inherently linked to the degree to which norms are internalized.

In the Ultimatum Game the proposer will split the sum of money in a way that will maximize her gain. To do so, she will have to take into account her beliefs about the recipient (that he too will try and make as much money as possible) and the probability that he will not accept the offer (which should be null). According to this calculation, she should share with the other player only a minimal fraction of the total sum. She should expect that the recipient would accept anything he was offered, as anything above a gain of zero would be a way to maximize his gain.

Results obtained from the Ultimatum Game show a clear deviation from this standard theoretical solution. In fact, in general, most proposers often make much larger offers than predicted, thus acting in a suboptimal and irrational way. On the other hand, recipients reject very small offers that may seem insulting relative to some standard of fairness (e.g., Rabin, 1993; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). These results are usually interpreted as evidence that behavior is often driven by social emotions and not just by the need to maximize personal gain (e.g., Sanfey et al., 2003; van't Wout, Kahn, Sanfey, & Aleman, 2006). Other-regarding preferences, which are guided by fairness and equality motives, play as big a role as self-regarding preferences (Bowles, 2006; de Quervain et al., 2004; Fehr & Gächter, 2002). Thus, players' acceptance of social norms (e.g., fairness) and their enforcement as driven by emotional responses to others' behavior induce a divergence between the players' actual behavior and the rational behavior.

Studying Social Decision Making with Noninvasive Brain Stimulation

Van't Wout et al. (2005) hypothesized that the DLPFC is crucial for determining the strategy of rejecting unfair offers, and predicted that temporary disruption of right DLPFC activity would shift the strategy towards higher rates of acceptance and/or interfere with rejection of unfair offers. They applied rTMS in an offline protocol over the right DLPFC (area F4), with participants receiving both real and sham (with a placebo coil over F4) stimulation in the same session separated by a 30 min interval.

Immediately after stimulation, they performed a version of the Ultimatum Game, always playing the responder role. A picture of the proposer was shown at the beginning of each trial. Both offers (fair or unfair, with three different levels of unfairness) and proposers (a different proposer in each trial) were randomly presented and participants were asked to respond as fast as they could to the offer by pressing the accept or the reject button (see Figure 9.1).

When restricting the analysis to unfair offers, rTMS condition (real vs. sham) significantly interacted with decision (accept vs. reject). After real rTMS, indeed, participants were slower at rejecting unfair offers and showed a trend towards higher acceptance. Although this study had no control site or control task, it showed that rTMS affected only the unfair condition, as predicted, and not the fair one. Moreover, its conclusions were later strengthened and extended in a different laboratory. Knoch, Pascual-Leone, Meyer, Treyer, and Fehr (2006b), indeed, tested with offline rTMS two alternative hypotheses on the role of the DLPFC in rejecting unfair offers in the Ultimatum Game. The first hypothesis considered the DLPFC as implementing fair behavior overriding selfish motives, thus predicting an increase in the acceptance rate of unfair offers after disruption of the DLPFC. The second hypothesis predicted an increase in the rejection rate of unfair offers due to a limitation of cognitive control over the fairness impulses after disruption of the DLPFC. Results showed a significant increase in the acceptance rate of unfair offers after right rTMS in comparison to left rTMS or sham (placebo stimulation) treatment groups. Interestingly, disrupting the DLPFC with rTMS did not alter fairness judgments about received offers but it disrupted reciprocal fairness behavior. Stimulation on the right DLPFC determined no difference between the response time between accepting fair offers versus unfair ones; in contrast, left DLPFC rTMS and sham groups took longer to accept unfair offers vs. fair ones.

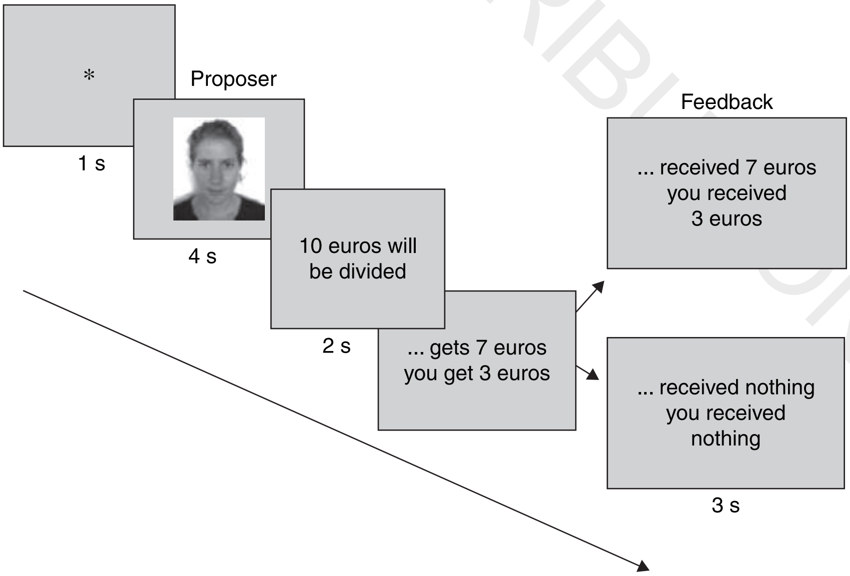

FIGURE 9.1 Example trial of the Ultimatum Game employed by van't Wout et al. (2005).

This suggested that a disruption of the right DLPFC reduced the conflict between self-interest and fairness and increased the automatic nature of the behavioral response.

To test for the differential role of two concurrent fairness motives – reciprocity and inequality aversion – Knoch et al. (2006b) added also a within-subject control condition in which the offers were not made freely by a human counterpart, but participants were informed that proposers were forced to follow random computer assignments. Behavioral responses in the computer offer condition revealed no differences between treatments. Notably, the acceptance rate of the right rTMS group increased from 48% in the human offer condition to 78% in the computer offer condition. Thus, the right rTMS group behaved normally when reciprocity motives were not present. Therefore, according to Knoch et al. (2006b) the main function of the DLPFC is to implement behavior based on fairness considerations overriding selfish motives and impulses.

Corroborating results are found in the study by Knoch, Nitsche, Fischbacher, Eisenegger, Pascual-Leone, and Fehr (2008). In this study they used cathodal tDCS to the right DLPFC with a large group of subjects (see Figure 9.2). In each experimental session, a group of responders (right cathodal tDCS and sham) played in the Ultimatum Game with a group of anonymous receivers. The results indicated that the group of subjects that received right tDCS stimulation was more

FIGURE 9.2 Experimental setting employed by Knoch et al. (2008). Groups of participants performed the task in parallel and interactively in a given experimental session. An experimenter sat between pairs of responders to control for the correct functioning of the tDCS devices.

willing to accept unfair offers, as shown by a higher rate of acceptance. Thus, stimulation on the right PFC induced a reduction in the typical punishment behavior in the Ultimatum Game.

Studying Risk-Taking Behavior with Noninvasive Brain Stimulation

If the Ultimatum Game provides a measure of the ability to override immediate urges in the context of social interactions, then Risk Tasks provide a measure of self-control in individual decision making (Knoch & Fehr, 2007). That right PFC may exert a control role on risk-taking behavior is already suggested by neuropsychological observations (e.g., Clark, Manes, Antoun, Sahakian, & Robbins, 2003), however only in recent years has the hypothesis undergone direct testing in the normal brain. Two studies, one with rTMS (Knoch et al., 2006a) and one with tDCS (Fecteau, Knoch, Fregni, Sultani, Boggio, & Pascual-Leone, 2007a), employed a risk task in which participants have to decide between a relatively safe choice providing a low reward with high probability, and a risky choice providing a high reward with low probability (see Figure 9.3).

Their target was to win as many points as they could during the experiment. Had their bet resulted in a loss, the same amount of points as they might have won would have been taken from their total count. Knoch et al.'s (2006a) results showed that the number of points earned was significantly dependent on stimulation condition, which in turn was consequential to the different proportion of risky choices. Right DLPFC stimulation, indeed, inflated the preference for the high-risk option compared to sham and left DLPFC stimulation. For every group, instead, the percentage of safe choices increased as the balance of reward increased (i.e., the difference in reward between the high-risk and low-risk option decreased). Knoch et al. (2006a), after dismissing alternative interpretations (see also Knoch & Fehr, 2007), therefore concluded in favor of a crucial role for right DLPFC in suppressing superficially seductive but risky options. Interestingly, Gianotti et al. (2009), by using resting-state encephalography, have recently discovered a link between tonic activity level in the right PFC and individual risk-taking behavior. More precisely, individuals with higher baseline cortical activity were more risk-averse.

Fecteau et al.'s (2007a) results obtained with a different technique, tDCS, also provide converging evidence. By upregulating right DLPFC activity while downregulating left DLPFC activity with concomitant right anodal/left cathodal tDCS, they were indeed able to decrease risk-taking behavior in a group of participants while they were performing the above-mentioned Risk Task. Compared to sham and left anodal/right cathodal tDCS groups, right anodal/left cathodal participants chose the safe option more often and earned many more points. In other word, Fecteau et al. (2007a) were able to reverse the behavioural effect that Knoch et al. (2006a) had found with low-frequency rTMS over right DLPFC. However their right cathodal /left anodal condition did not increase risk-taking behavior, which might be due to a difference in the neurophysiological impact of the two techniques, and suggests that it is not possible to draw simple inferences about the

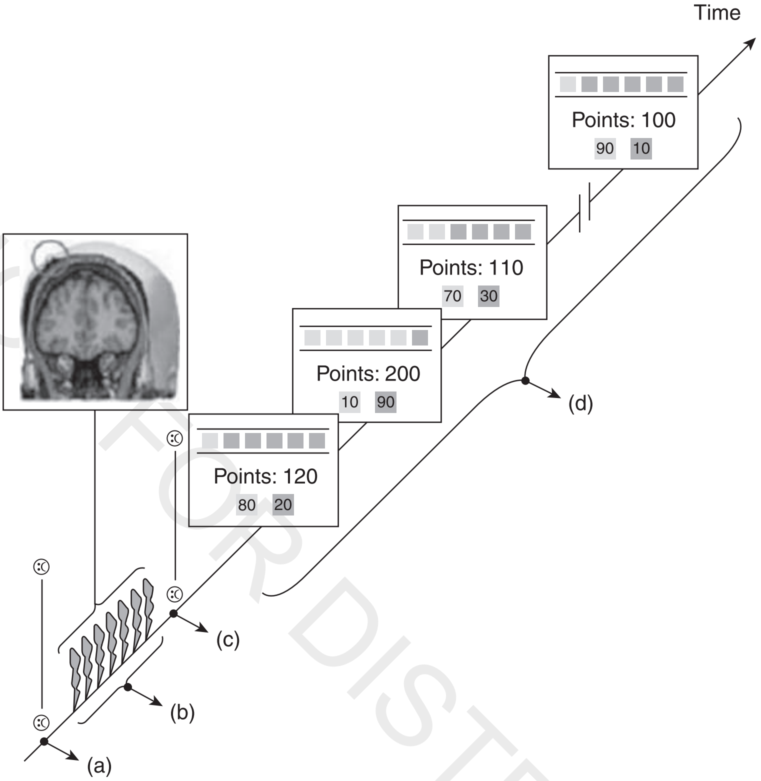

FIGURE 9.3 Experimental protocol employed by Knoch et al. (2006a). Mood self-rating (a, c) was required of participants before and after 1 Hz offline rTMS over left or right DLPFC (b). In the following task (d), the ratio of pink and blue boxes (i.e., the level of risk) changed from trial to trial, and the numbers inside the two bottom boxes show the reward and punishment sizes associated with each colour (i.e., the balance of reward). The larger reward and penalty were associated with choice of the high-risk prospect, and vice versa for the low-risk prospect (a typical conflict in risk-taking situations). The participant's task was to select one of the two bottom boxes in order to indicate the color of the upper box thought to hide the winning token.

underlying mechanisms of action in different techniques based only on the direction of their net behavioural effect. Moreover, tDCS was applied to both right and left DLPFCs at the same time in Fecteau et al.'s (2007a) study, whereas Knoch et al. (2006a) applied rTMS unilaterally.

A tDCS study tackling similar issues but with a different task was conducted by Fecteau et al. (2007b). They measured risk-taking behavior by the Balloon Analog Risk Task (BART; see Figure 9.4). In BART, participants have to make a choice in a context of increasing risk. A computerized balloon, which can explode at any moment, has to be inflated by pushing a pump, and participants can decide after any pump if they want to continue or stop. Each pump is associated with the same

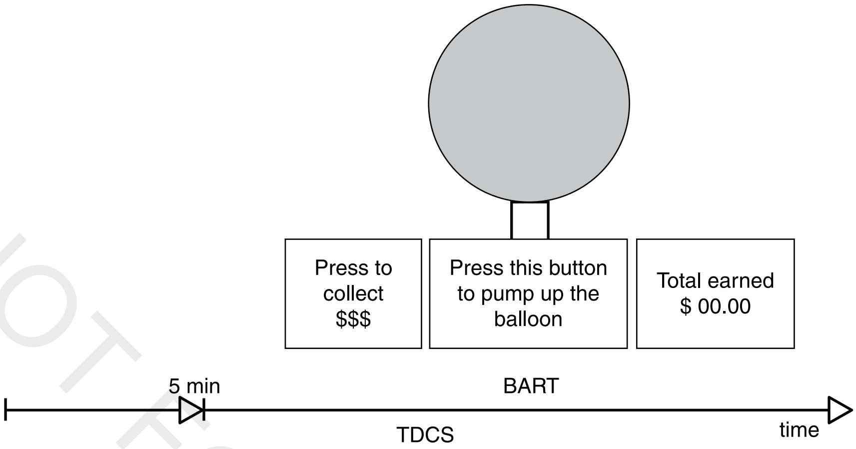

FIGURE 9.4 Experimental protocol employed by Fecteau et al. (2007b). Participants first received 5 min of tDCS without performing any task. After 5 min, the Balloon Analog Risk Task (BART) started, while stimulation went on.

monetary reward, but if the balloon explodes all of the money accumulated up to that point is lost. In other words, the probability of losing money, as well as the potential loss, increases with each pump and is difficult to predict since each balloon has a different explosion point. Quite surprisingly, both groups receiving bilateral stimulation, and not only the right anodal/left cathodal group, showed more cautious behavior compared to the sham group. Unlike the sham group, moreover, they did not show the normal increase in the number of risky choices that is usually found with time. Finally, all participants receiving bilateral stimulation earned less money than participants receiving sham stimulation. No tDCS effects were found when unilateral anodal stimulation was applied to either the left or the right DLPFC.

CONCLUSION

The major novelty of the methodology described here is that it studies human behavior at multiple levels and from multiple perspectives, adopting as a unifying principle the conceptual framework of game theory and decision theory (individual decision making). We expect this initiative to foster a new interface between theory and experimentation, between mathematical models and brain function. In addition, the results may provide additional means for diagnosis/measurement of the extent of impairment due to prefrontal lobe damage, and provide patients with new rehabilitation tools to help them lead more normal or successful lives. Prefrontal dysfunction is a crucial component of several mental conditions, such as schizophrenia and drug addiction. The mechanistic level of explanation may help a finer understanding of the physiology and therefore the pathology of those areas, and form the basic research foundations for a new generation of treatments.

Finally, on a more philosophical note, the results of noninvasive brain stimulation studies on decision making in conjunction with other work in this area may give us greater insight into precisely what it means to be rational – a question that, as the divergence between the prescriptions of game theory and actual play in games suggests, is far from clear.

UNRAVELLING THE PROCESS OF CHOICE WITH NONINVASIVE BRAIN STIMULATION

An additional interesting development consists of the possibility to trace the neural fate of information processing during a task by employing a dual or multiple coil protocol. This approach allows researcher to probe the flow of information between areas and the necessity of connected areas and connection between areas for a given task. This approach would therefore allow to go beyond the use of noninvasive stimulation for simple localization purposes and upgrade the level of analysis to circuit dynamics. A more refined use of noninvasive technique will enable to better describe the complex underpinnings of decision processes. This research will bridge the gap between the different levels of analysis, from single areas (single coil protocol) to networks (dual or multiple coil protocol). The use of a dual or multiple coil protocol will permit validation of the model-based analyses and an in-depth analysis of the brain signals in different stages during decision making (i.e., process tracing). With the results of this research it will be possible to build mathematical and computational models of the processing underlying decision making (Simon, 1979, 1982); this will contribute to building a neural, behavioral, and theoretical foundation for psychological and economic decision theory. As stated by Benhabib and Bisin (2005, p.):

> The traditional method of decision theory, founded on revealed preferences, restricts its focus on predicting and explaining choice and is agnostic about the process underlying choice itself. Recent research in economics (typically under the heading of neuroeconomics or of behavioral economics) aims instead at developing joint implications on choice as well as on processes.

LIMITATIONS

Of course there are limits in the application of noninvasive brain stimulation techniques to the study of decision making. As already mentioned, decision making is likely supported by a complex network of interacting areas. Some of them are close to the cortical surface, whereas other are deeper and subcortical. Due to the rapid decay of the magnetic field and dissipation of electrical currents, neither TMS nor tDCS can directly reach subcortical areas. And even if technology could improve their depth of stimulation (Wagner et al., 2009), deep areas could not be targeted without stimulating at the same time all the neural tissue that lies between them and the stimulator device. On the other hand, if it is reasonable to assume that the effect is maximum at the stimulation site, it might well be that concomitant behavioral effects are induced by upregulation or downregulation of distant areas that are synaptically connected with the neuronal populations under the stimulation site. Studies of regional cerebral blood flow changes induced by brain stimulation (e.g., Eisenegger, Treyer, Fehr, & Knoch, 2008; Knoch et al., 2006a) can certainly complement behavioral studies and provide useful clues to an appropriate interpretation of behavioral effects. Combining fMRI with brain stimulation and behavioral tasks seems even more promising an approach, since it allows changes in task performance to be correlated with regional BOLD changes on an individual basis; however, one has to keep in mind that whereas a causal link may be drawn between brain stimulation and behavioral changes, the same does not hold true for brain activations and behavioral changes (Sack, 2010).

SUMMARY

In summary, noninvasive stimulation techniques are a powerful tool that can provide strong but complementary evidence with respect to neuroimaging methods, and their potential may be best exploited when they are used in combination with other techniques. Finally, it should not be neglected that, irrespective of their theoretical basis and interpretation, behavioral effects obtained with noninvasive stimulation that shift impulsive behavior towards safer prospects can be desirable in clinical settings too. In turn, the long-term effects of such applications can inform theoretical models of decision making in both the healthy and pathological brain, and elicit additional research hypotheses.

FUTURE DIRECTIONS OF NONINVASIVE BRAIN STIMULATION APPROACHES TO SOCIAL COGNITION

Neuroscientific approaches to social cognition provide crucial information about the brain regions and processes involved in the perception of social stimuli and high-level strategic thinking in interactive settings. In this chapter we discussed studies of the mechanisms of choice strategies from a game theory perspective using noninvasive brain stimulation methodologies. This research is conducted using a fundamentally multidisciplinary approach drawing on game theory, behavioral economics, and cognitive neurosciences. It applies robust methods and findings from behavioral decision theory to study the brain structures that contribute to decision processes. Future research in this direction will be useful for the definition and understanding of basic components of social decision making, such as: the amount and type of rationality involved in the interactions; the process of belief formation, that is, how people generate beliefs about the rationality of the others; the cognitive and processing aspects; and the process of learning in social settings.

RECOMMENDED READING LIST

For a general introduction to the use of noninvasive stimulation in cognitive neuroscience and more technical details, see:

- Paulus (2003) – transcranial direct current stimulation (tDCS).
- Rusconi & Bestmann (2009) – the contribution of TMS to structure–function mapping in the human brain; action, perception, and higher functions.
- Wagner et al. (2007) – noninvasive human brain stimulation.
- Wassermann et al. (2008) – handbook of transcranial stimulation.

NOTE

1. Game theory is based on equilibrium concepts such as the Nash equilibrium and refinements such as subgame perfection. Equilibrium is a situation in which no one has the incentive to deviate, thus no one should move away. Therefore, it is a possible solution to the game. A game is a representation of an interactive problem between players. There are different ways of representing (describing) interactive situations and thus solving the resulting game theoretic problem. This representation concerns: (i) the structure of the interaction, which specifies the set of available strategies for each player and how players evaluate their payoff (payoff function); (ii) the order in which they move – whether actions are simultaneous (static games) or sequential (dynamic games); and (iii) the information structure – there is complete information when all players have full information about the structure of the game, the payoff function (i.e., the function that determines the player's payoff from the combination of possible actions), while incomplete information refers to the situation in which one player does not know the payoff function of the other players (e.g., at an auction, where the willingness to pay is unknown). Situations with static and complete information can be represented by games in strategic forms and solved with Nash equilibrium; interactions in dynamic settings (sequential and repeated interaction) can be represented by extensive form games and solved using the concept of subgame perfection; situations with incomplete information need more complex game-theoretic tools, such as the Bayesian Nash equilibrium; and incomplete information and dynamic games need more restrictive equilibrium refinements such as the perfect Bayesian Nash, the sequential equilibrium, and the trembling hand perfect equilibrium. Thus, over the years game theory has provided powerful tools for modeling rational behavior in complex interactive contexts.

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