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Chapter 8

Extinction as a deficit of the decision-making circuitry in the posterior parietal cortex

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Abstract

Extinction is a common neurologic deficit that often occurs as one of a constellation of symptoms seen with lesions of the posterior parietal cortex (PPC). Although extinction has typically been considered a deficit in the allocation of attention, new findings, particularly from nonhuman primate studies, point to one potential and important source of extinction as damage to decision-making circuits for actions within the PPC. This new understanding provides clues to potential therapies for extinction. Also the finding that the PPC is important for action decisions and action planning has led to new neuroprosthetic applications using PPC recordings as control signals to assist paralyzed patients.

INTRODUCTION

Hemispatial neglect is a common disabling condition that frequently occurs after unilateral brain damage, particularly of the right posterior parietal area (Stone et al., 1991; Bisiach and Vallar, 2000; Heilman et al., 2000; Karnath et al., 2002; Parton et al., 2004; Vallar and Bolognini, 2014; Vallar and Calzolari, 2017). Patients with neglect often fail to be aware of stimuli located on the side of space, their body, or both, contralateral to the side of the hemispheric lesion (contralesional, for example, the left side for patients with right-brain damage), and attend instead to stimuli located on the same side as their brain damage (ipsilesional side). In extreme conditions, they even fail to eat the portion on the left half of their plates, to shave and to dress the left side of their body, and even show the bodily delusion of failing to recognize their contralesional limbs as their own – i.e., somatoparaphrenia (Gerstmann, 1942, and see Vallar and Ronchi, 2009, for review).

A less severe consequence of unilateral parietal damage is extinction: a neurologic disorder that is characterized by the inability to perceive contralesional stimuli, but only when a simultaneous ipsilesional stimulus is also presented (Bender and Teuber, 1946; Wortis et al., 1948; Critchley, 1949). Historically extinction was considered a mild form of hemispatial neglect that is caused by a selective attention deficit after brain damage (Critchley, 1953; Mattingley, 1999; Vuilleumier and Rafal, 2000). According to this view, the two brain hemispheres compete through inhibitory interactions to direct spatial attention to the contralateral hemispace. Following brain damage, the intact hemisphere becomes hyperactive due to reduced inhibition from the lesioned hemisphere, shifting attention to the ipsilesional hemispace (Kinsbourne, 1993; Rossi and Rossini, 2004). When two similar stimuli are presented simultaneously in both visual fields, the ipsilesional one usually wins the competition.

However, more recent evidence suggests that extinction is a neurologic disorder distinct from hemispatial neglect (Bisiach, 1991; Vallar et al., 1994). It may represent a deficit in the decision-making circuitry rather than in spatial attention (Christopoulos et al., 2015b;

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Kubanek et al., 2015). In large part, this proposal is based on findings showing that the parietal cortex is involved not only in processing awareness, spatial perception, and attention, but also it is within a network for making motor decisions (Platt and Glimcher, 1999; Gold and Shadlen, 2007; Andersen and Cui, 2009; Cisek, 2012). Additionally, reversible pharmacologic inactivation studies in nonhuman primates (NHPs) provide direct evidence that there is effector-specificity for decision making in the posterior parietal cortex (PPC) (Christopoulos et al., 2015b; Kubanek et al., 2015). Hence, extinction could be alternatively viewed in many cases as a bias in decision making rather than a bias in spatial attention.

In this chapter, we discuss new evidence that views extinction as a deficit in the decision-making process. The first section presents insights about the pathophysiology of extinction from clinical studies in human patients. Further it reviews clinical studies on extinction in the motor, visual, auditory, and tactile modalities.

The second part introduces and compares the two prevailing theories in decision making–the sequential (Padoa-Schioppa, 2011), and the parallel (Cisek and Pastor-Bernier, 2014) theory. The first views decision and action as two separate cognitive processes, in which action planning begins only after a decision has been made (Padoa-Schioppa and Assad, 2006; Padoa-Schioppa, 2011). The brain first integrates all relevant factors (e.g., expected reward, potential risks, action costs) into a single variable that reflects the subjective value of each option. The alternative with the highest subjective value is then selected. Once a decision is made, the brain generates the appropriate action plan to implement the choice. In an apparent conflict with the sequential theory, a series of motor decision studies have reported decision-related activity in cortical and subcortical regions that are involved in planning and executing actions. These findings led neuroscientists to propose that decision and action are coupled and tightly integrated processes (Cisek and Kalaska, 2005; Cisek and Pastor-Bernier, 2014). According to this parallel theory, the brain prepares in parallel multiple action plans that compete for selection, before choosing one of them to execute (Cisek, 2007; Thura and Cisek, 2014). We discuss how this theory can provide new conceptual advances in understanding the mechanisms underlying extinction.

The last section focuses on potential rehabilitation strategies using decision-making approaches and brain stimulation treatments. It also shows how the action-planning circuitry in the PPC can be harnessed for brain–machine interface (BMI) applications for neural prosthetics. Despite partial recovery in the first months after parietal damage (Lawson, 1962; Levine et al., 1986; Stone et al., 1992; Pizzamiglio et al., 1998; Rengachary et al., 2011), many of the patients suffer from unilateral spatial neglect and extinction symptoms for a long period of time and therefore need specific treatment. The decision-making approaches aim to restore the choice balance by either increasing the reward or reducing the action cost for choices in the contralesional hemifield (Wilke et al., 2013). The extinction symptoms could also be transiently alleviated via brain stimulation treatments that aim to restore the dynamic balance between the two hemispheres (Oliveri et al., 2001; Sparing et al., 2009). Finally, novel BMI techniques developed in our lab could potentially use the decision-making apparatus, particularly the outcome plans of decisions, for neural prosthetic applications (Aflalo et al., 2015).

EXTINCTION PRESENTATION AND CAUSES OF EXTINCTION

Clinical neurology of extinction

Unilateral spatial neglect is a heterogeneous syndrome (Barbieri and De Renzi, 1989; Vallar, 1998; see Chapter 14) with varying degrees of multimodal sensory and motor deficits leading to the inability to spontaneously perceive, explore, and interact in the space contralateral to the lesioned hemisphere, despite intact primary sensory input and/or motor output (Andersen et al., 2014). Extinction is a component frequently seen in conjunction with spatial neglect in which a patient is able to independently respond to a sensory stimulus in both the ipsilesional and contralesional space. However, when two sensory stimuli are presented simultaneously, typically one in the ipsilesional and one in the contralesional side of space, the patient is only able to consciously perceive and report the ipsilesional and not the contralesional stimulus.

Similarly, extinction can also be seen in the motor domain, where a patient is able to perform motor tasks independently with either limb, but not with the contralesional limb when asked to perform movements simultaneously with the two limbs; motor extinction may occur without associated sensory deficits (Valenstein and Heilman, 1981). The neurologic findings described above are often referred to in clinical practice as extinction on double simultaneous stimulation testing.

Extinction is a unique component of spatial neglect in that is a phenomenon present only when there is competition in the brain to perform tasks simultaneously. It has been postulated that extinction is in fact an exaggeration of the brain's natural response to process several competing stimuli in the environment (Duncan et al., 1997; Driver and Vuilleumier, 2001). Extinction has been described in multiple sensory modalities, including visual, auditory, and tactile, and has been debated to possibly occur to a limited degree in olfactory and gustatory modalities (Brozzoli et al., 2006; Gallace and Spence, 2008; Jacobs et al., 2012).

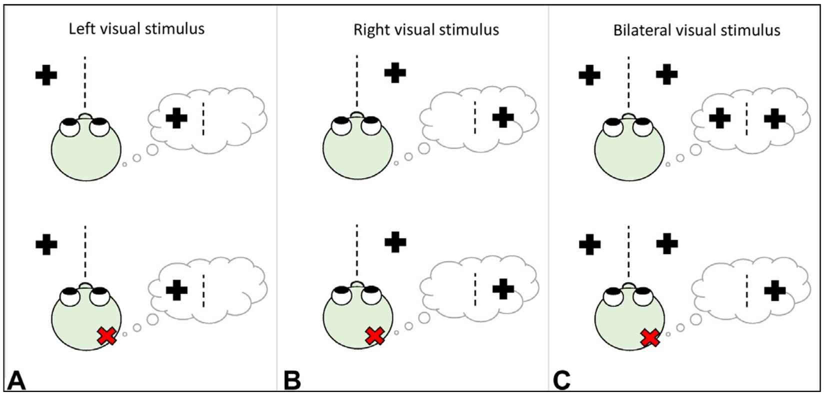

Fig. 8.1. Schematic of visual extinction. (**A**) Left-sided visual stimulus shown to control subject (top) and patient with right hemisphere lesion (bottom): both report the left-sided stimulus. (**B**) Right-sided visual stimulus shown to control subject and patient with right hemisphere lesion: both report the right stimulus. (**C**) Left- and right-sided (double) simultaneous stimulation: control subject can report both the left-sided and the right-sided stimuli, while patient with right-hemisphere lesion can only report the right-sided stimulus, thus extinguishing the left stimulus.

Motor extinction has also been described in right-brain-damaged patients as (1) the inability to perform movements with the contralesional left hand, when simultaneous movements of the right hand are required, in both the ipsilesional and contralesional space (left canonic body extinction); and (2) with either the ipsilesional right and the contralesional left hand in the contralesional left side of space (left-space extinction), depending on the location of the lesion (Hillis et al., 2006; Heidler-Gary et al., 2013).

While discrete lesions within designated small anatomic areas can be used to study extinction in NHPs, patients often display symptoms of spatial neglect in addition to extinction, owing to the fact that the mechanism of damage to the parietal lobe in patients often covers a large anatomic extent. Neglect can also be multimodal, being more severe in the visual than in the tactile modality, and may occur in diverse sensory modalities (auditory, visual, somatosensory modalities: Bisiach et al., 1984; Gainotti, 2010; Mancini et al., 2011; Gutschalk and Dykstra, 2015). Damage to the parietal lobe in humans can be caused by numerous pathologic mechanisms, including ischemic and hemorrhagic strokes (Vallar and Perani, 1986; Leibovitch et al., 1998), traumatic brain injury (Chen et al., 2016), neurodegenerative diseases (Silveri et al., 2011), brain neoplasms (Vallar and Perani, 1987; Shallice et al., 2010), congenital malformations, and other intracranial lesions, such as those due to autoimmune diseases, such as multiple sclerosis (Gilad et al., 2006).

Clinical presentation of extinction

VISUAL EXTINCTION

Visual extinction is commonly seen in patients with neglect and extinction both in visual perception and in performing visually guided tasks. Visual extinction may present, for example, in a patient with right parietal damage who is able to read columns in a newspaper when present solely on the left or solely on the right side of a newspaper, but when presented on both sides of the page, he or she will only read from the right side (Wilson et al., 1987). At the bedside, visual extinction has classically been demonstrated through the presentation of double simultaneous stimuli by the examiner (Bisiach and Faglioni, 1974). For example, a patient with a right-sided parietal lesion with visual extinction may have fully intact visual fields on confrontational testing, be able to identify a visual stimulus (such as an examiner's finger) when presented independently by the examiner in the left or right visual field (Fig. 8.1A and B), but, when the two stimuli are presented simultaneously, one finger in each visual field with the patient's gaze centrally fixed, the patient will only see the ipsilesional stimulus, in this case the right-sided stimulus, thus "extinguishing" the contralateral stimulus (Fig. 8.1C).

AUDITORY EXTINCTION

Auditory extinction may be more subtle than visual extinction, but it can present and be tested in a similar fashion to visual extinction. Auditory extinction can grossly be tested at the bedside by producing a sound, such as the examiner rubbing the fingers together, next to each ear independently, and then rubbing the fingers next to both ears simultaneously. Similar to visual extinction, the patient will identify the finger rub independently on both the right and left side, but he or she will only identify the sound in the ipsilesional ear when there is double simultaneous finger rubbing.

More formal auditory testing can be done using a dichotic speech test where the patient wears headphones and is asked to repeat the word said into the left or right ear. When patients are given a word in each ear independently, they will be able to repeat the word, for example, "shoe" in the ipsilesional ear and "cat" in the contralesional ear, but when those words are said simultaneously, patients will only repeat the word in the ipsilesional ear, in this example "shoe." In addition, when patients are played the same auditory cue into each ear independently they will correctly localize the cue to the left or right side, but when the same auditory cue is played simultaneously on both sides, they will localize the sound to the ipsilesional side (Gutschalk and Dykstra, 2015).

TACTILE EXTINCTION

Tactile, or somatosensory, extinction is also observed in patients and can be tested at bedside using double simultaneous stimulation. Patients with tactile extinction will individually locate a fine touch on both the contralesional and the ipsilesional side when touched independently, but, when touched simultaneously, they will only perceive the touch on the ipsilesional side. When testing tactile extinction, examiners have noted that there can be cross-modality extinction in which a patient may extinguish an independent touch on the contralesional side if asked to look at the ipsilateral side. For example, patients with a right-hemisphere lesion may, with the eyes closed, be able to locate fine touch on both the right and the left limb, but not identify the sensation of touch on the left limb when they are touched simultaneously. If patients then open their eyes and are instructed to look at their right limb, while being independently touched on the left limb, they may not report sensation on the left limb (Gallace and Spence, 2008).

MOTOR EXTINCTION

Two types of motor extinction have been described in the literature, one in which the contralesional body is extinguished in simultaneous bimanual tasks regardless of its location in space (egocentric frame of motor extinction), and the other in which the subject has motor extinction of either the contralesional or ipsilesional limb in a bimanual task depending on what side of space the patient is performing the task (spatial frame of motor extinction) (Hiilis et al., 1998; Heidler-Gary et al., 2013). For example, in an egocentric frame of motor extinction, a patient with right-hemisphere brain damage would be able to hold a cup of water alone in the left hand and right hand, but when given a cup to hold in both hands, the patient will drop the cup in the left hand always regardless of whether the left hand is on the left side or on the right side of space with respect to the midline of the body.

Alternatively, in a spatial frame of motor extinction, a patient with a right-sided brain lesion, when presented with two cups of water, would drop the cup from the left hand when it is on the left side of the body in space, but if the arms were crossed, the patient will drop the cup from the right hand as it is now on the left side of bodily space.

These two types of motor extinction were demonstrated by Heidler-Gary et al. (2013) in a series of 93 patients with subacute right-hemispheric infarcts by having the patients click a button concealed from view with their left hand independently, right hand independently, left hand on left side of the body, and right hand on right side of the body simultaneously, and finally with the arms crossed with the left hand on the right side of the body, and the right hand on the left side of the body simultaneously. Patients with more dorsal parietal lesions extinguished movements with either hand in the left side of space, in the bimanual test (left spatial extinction), while patients with more ventral temporal and subcortical temporal lesions extinguished left-hand movements in either side of space (left body extinction) (Heidler-Gary et al., 2013).

Clinical causes of extinction

While unilateral spatial neglect and extinction can be seen either after right-hemisphere or left-hemisphere damage, they more commonly occur after right-hemisphere brain damage (Critchley, 1949; Schwartz et al., 1979; De Renzi, 1982; but see Ogden, 1985). Becker and Karnath (2007) studied patients with unilateral lesions in either the left side or right side of the brain and found that visual neglect and extinction were significantly higher in patients with right-sided lesions. Their study showed that patients with left-sided brain lesions had a 2.4% prevalence of visual neglect and a 4.9% prevalence of visual extinction. In comparison, patients with right-sided brain damage showed visual neglect in 26.2% and visual extinction in 24.3% (Becker and Karnath, 2007).

A second study by Chechlacz and colleagues (2014) of 454 patients with unilateral subacute strokes confirmed that visual neglect and extinction were more prominent in patients with right-sided brain lesions, but with the qualification that the difference in rates of spatial neglect and extinction after left- versus right-sided damage was more pronounced with lesions affecting the middle cerebral artery and the posterior cerebral artery vascular territories, but not other vascular territories. They also tested tactile neglect and extinction and found that they were more common after right-sided brain injuries.

This study also found that, when present, the severity of visual and tactile neglect and extinction was the same after both left- and right-sided brain lesions. Interestingly they found that lesions of the left hemisphere had an increased prevalence of visual over tactile extinction while right-sided lesions produced both modalities of visual and tactile extinction at a similar rate (Chechlacz et al., 2014).

A study done by De Renzi and colleagues (1984) on auditory extinction in 144 patients with unilateral strokes found that auditory neglect was more common, but not significantly so, in right-hemisphere-damaged patients, with 45% of patients with right-sided lesions and 36% of patients with left-sided lesions displaying auditory extinction. The study, however, did find that extinction secondary to right-hemisphere strokes lasted significantly longer than those caused by left-hemisphere strokes (De Renzi et al., 1984).

In patients, the etiology of damage to the right and left hemisphere of the brain, most notably the parietal lobe and its projections, is numerous, including vascular, neoplastic, traumatic, infectious, and autoimmune processes. The most common cause of parietal lobe damage leading to spatial neglect and extinction is stroke, particularly in the vascular territory of the middle cerebral artery (Chechlacz et al., 2014; Li and Malhotra, 2015). While the prevalence of extinction or neglect has not been studied, strokes are the fifth leading cause of death in the United States and approximately 750,000 people suffer from new or recurring strokes each year (Mozaffarian et al., 2016).

With the increase in improved awareness of stroke symptoms in the population, the use of intravenous thrombolytic medications, and the improvement of intra-arterial thrombectomy technology, the number of stroke survivors has increased over the past several years (Mozaffarian et al., 2016), thus increasing the number of survivors with neurologic disability, including spatial neglect and extinction. Approximately 85% of strokes are ischemic in nature, and infarcts affecting the parietal cortex can be seen covering a specific vascular distribution of a single artery, such as the middle cerebral artery, which typically perfuses the lateral surface of the cortex, but spares the anterior parietal cortex and frontal lobe, which is supplied by the anterior cerebral artery.

Likewise, ischemic strokes due to hypoperfusion of brain, such as that caused by cardiac arrest or severe carotid stenosis, lead to damage in the "watershed" areas of the brain at the junction of two major vascular territories. Watershed lesions in the zone between the middle cerebral artery and posterior cerebral artery can lead to infarction in the temporal parietal junction, including the PPC (Caplan and Van Gijn, 2012). Occlusion of the posterior circulation of the brain due to vertebrobasilar artery disease can also lead to damage of the PPC (Montero et al., 1982). Within individuals, however, anatomic variations exist within the circle of Willis and within peripheral branches of their cerebral vascular tree, leading to heterogeneous damage, and hence a wide range and multifaceted combination of clinical symptoms (Lang et al., 1995). Rarely, some small lesions, for example, stereotactic thalamic lesions performed for the relief of dyskinesias, can lead to isolated spatial neglect or extinction (Hiilis et al., 1998), but it is much more common for them to occur with a combination of other deficits by the larger lesions described above.

DECISION MAKING

Decision making is a fundamental cognitive process of human behavior by which an option is selected among a set of alternatives based on subjective preferences. Traditionally, it has been studied within the frame of economic theory and psychology (Fellows, 2004; Rolls, 2007). However, over the last decade it has attracted substantial interest in neuroscience. The reason is twofold. First, the study of decision making is considered a window to understanding cognition, because it exposes principles of neural processing that underlie a wide variety of high-order cognitive functions (Shadlen and Kiani, 2013). Second, decision making has important clinical implications. Many neurologic deficits, such as compulsive behavior, drug addiction, and gambling, point to damage of the brain mechanisms responsible for making decisions (Frank et al., 2007). Hence, it is important to understand the neural basis of decision making to develop efficacious therapies for brain disorders.

Although significant progress has been made over the past few years in understanding how specific brain regions are involved in decision making, there is still an ongoing debate on how the brain selects between alternative options. This debate has pitted the sequential theory versus the parallel theory (Cisek, 2012). The main argument between these two theories is whether decision and action are two separate cognitive processes, or whether decision and action are coupled into a parallel process.

Decision making as a distinct and separate cognitive process from action planning

Imagine that you are faced with the challenge of buying a new house. Different houses may vary in their price, size, location, amenities, number of rooms, distance from work, and more. How the brain integrates information from these disparate sources to evaluate the houses and select the best option remains a central question in

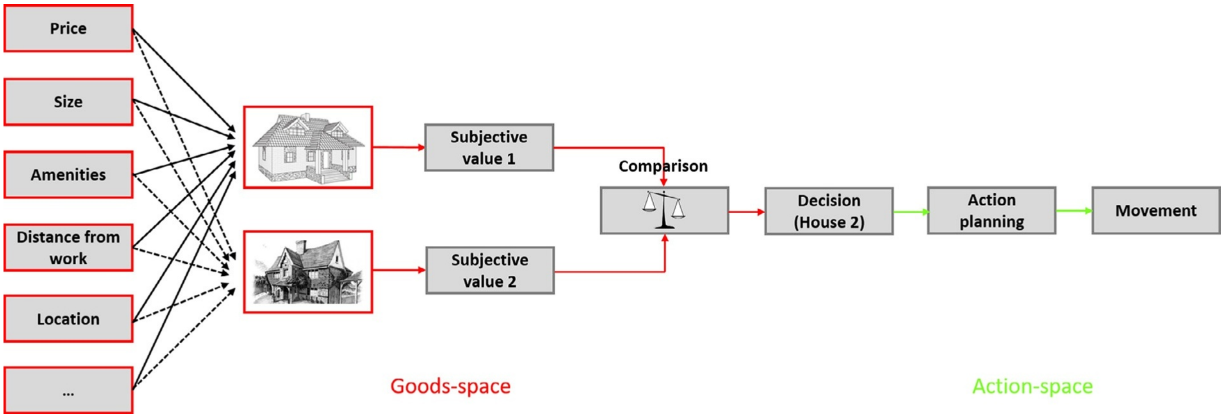

Fig. 8.2. Sequential theory of decision making in a hypothetic scenario of choosing between two houses. According to this theory, decision and action are two separate cognitive processes. The brain first integrates the decision factors of the alternative options (e.g., prize, size, amenities) into a single variable named subjective value. Subjective values are computed independently of one another, and without taking into account the sensorimotor contingencies of the choices (goods-space). The decision is made by comparing the subjective values within the goods-space. Once decided, the chosen option is transformed into an action plan to implement the choice (goods-to-action transformation in action-space).

neuroscience. Classic studies suggest that individuals first decide which house to buy, and then plan the actions to implement the choice (Tversky and Kahneman, 1981; Padoa-Schioppa and Assad, 2006; Padoa-Schioppa, 2011) (Fig. 8.2). According to this view, there is a central executive system in the brain that integrates all of the relevant factors of the house (price, size, etc.) into a subjective economic value. Decisions are made by comparing the subjective values of the available options. Only when a decision is made is the chosen option transformed into an action plan to implement the choice (goods-to-action transformation). Hence, the central axiom in this sequential theory is that the representation of the subjective value is abstract, in the sense that it does not depend on the sensorimotor contingencies of the choice; that is, the action required to implement the choice outcome. For instance, selecting house A over house B does not depend on whether you will drive or walk to the realtor after deciding which house to buy.

Since the famous case of Phineas Gage – the railroad construction foreman who survived severe damage to the brain after an iron bar pierced his left frontal lobe – clinical studies have pointed out that the central executive control system, in which decisions are made, resides in the prefrontal cortex (PFC) (Shallice and Burgess, 1991; Bechara et al., 1994; Fellows, 2006). However, it was only recently that neuroscientists started revealing the functional role of PFC in decision making. Neurophysiologic studies in animals showed that orbitofrontal cortex (OFC) and ventromedial PFC (vmPFC) neurons encode the abstract representation of the subjective values of the choice alternatives (for review, see Kennerley and Walton, 2011).

For instance, a recent study in NHPs showed that neurons in the OFC encode the subjective value of the reward being offered independently of the spatial configuration and the motor actions (Padoa-Schioppa and Assad, 2006). Along similar lines, other studies showed that OFC neurons integrate information from disparate sources, such as reward magnitude, outcome probability, and physical effort to obtain the reward into subjective economic values (Kennerley and Wallis, 2009). Additionally, a recent study reported that vmPFC neurons encode the subjective incentive value of an option, which is integrated with the action cost in anterior cingulate cortex, to compute an overall value for each alternative option (Bouret and Richmond, 2010).

The role of the prefrontal cortical regions in computing and comparing the subjective values for each choice in economic decisions has also been confirmed by human functional imaging. For instance, recent studies explored the tradeoffs between monetary reward and other decision-related factors, such as outcome probability (Levy et al., 2010), ambiguity (Hsu et al., 2005), time delay (Kable and Glimcher, 2007), and food type (Plassmann et al., 2007). Consistent with the neurophysiologic studies, activity in OFC was significantly correlated with the subjective values of the alternative options. Overall, these findings indicate that economic decisions emerge via a comparison of the abstract representation of the alternative options that takes place within the PFC.

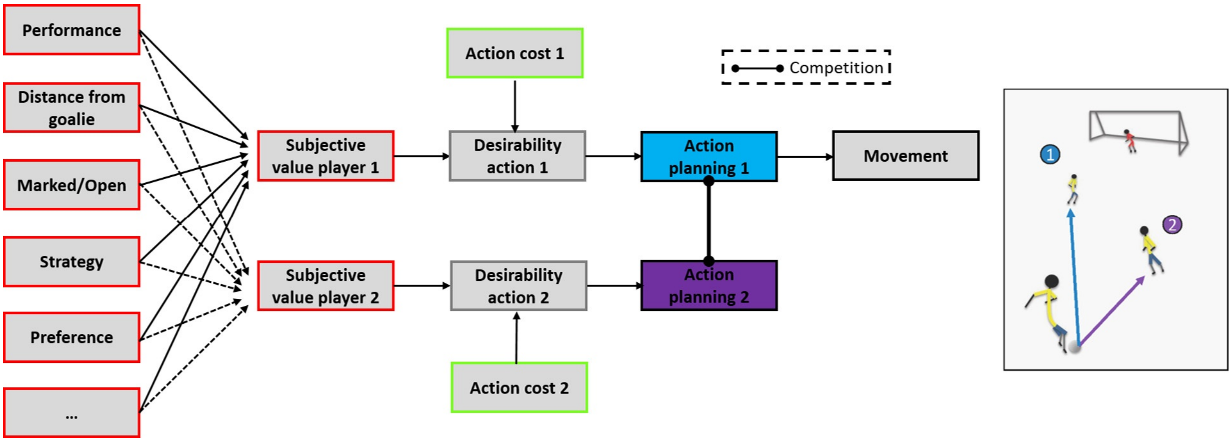

Fig. 8.3. Parallel theory in decision making in a hypothetic soccer game scenario. A player is looking for an open teammate to pass the ball or a chance to score. According to this theory, when choosing between multiple options, the brain generates concurrent potential actions that compete for selection and uses online information to bias the competition until a single goal is selected. In the current scenario, the brain plans two actions for the two alternative options, namely: pass the ball to the teammate 1 and pass the ball to teammate 2. Each of these two actions is characterized by the subjective value of the option itself and the cost required to execute this action. The subjective value is computed similar to the sequential model and integrates all the decision-related factors of the options. The subjective value is integrated with the action cost to compute the relative desirability value that reflects how desirable it is to select one action with respect to the alternative. The two potential actions compete for selection and the relative desirability values bias this completion until a single action is selected.

Decision making and action planning are coupled into a parallel process

Although values can be associated with choice alternatives in a manner independent of action planning, other decisions can be viewed as a process of action selection. For instance, consider the scenario of a soccer player who is moving the ball down the field looking for an open teammate to pass the ball to or a chance to score (right panel in Fig. 8.3). Abstractly, the player is faced with an action selection problem, in which he/she has to decide between competing options with limited time.

The fundamental difference between the soccer game scenario and the economic choice of buying a house, presented above, is that the first one takes place in dynamic environments – i.e., the availability and the value of the current actions can change with time and previous decisions. This requires the soccer player to plan actions while simultaneously evaluating the alternative options.

A growing body of evidence suggests that dynamic decisions and actions are coupled in a parallel process (for review, see Cisek, 2007; Cisek and Kalaska, 2010). Consider, for instance, a case in which the soccer player has the option to either pass the ball to a distant teammate 1 or to a nearby teammate 2 (Fig. 8.3). According to the parallel theory, the soccer player simultaneously plans two motor actions that compete for selection. Each of these actions is assigned with values related to the alternative option itself (e.g., teammates' performance, current distance of the teammates from the opponent's goal, strategy, marked vs. open teammates, and bias to choose one teammate versus the other), and with the cost required to implement this action (e.g., effort cost, required accuracy). For instance, it requires less effort to pass the ball to teammate 2, but distant teammate 1 is probably a better option, because he or she is closer to the opponent's goal. The action cost and the subjective value of the options are dynamically integrated into a desirability value, which reflects the attractiveness of an action and is used to bias the action competition (for a mathematic interpretation of the relative desirability function, see Christopoulos and Schrater, 2015). While the game progresses, the cost of the actions and the subjective values of the alternative options change continuously, biasing the action competition, until a single action is selected.

The parallel theory is consistent with a series of neurophysiologic studies showing that neurons in sensorimotor and premotor regions represent multiple potential actions long before a decision is made (Cisek and Kalaska, 2005; Cui and Andersen, 2007; Scherberger and Andersen, 2007; Kim et al., 2008; Klaes et al., 2011; Mysore and Knudsen, 2011).

For instance, Cisek and Kalaska (2005) recorded neural activity from dorsal premotor (PMd) while monkeys performed delayed "center-out" reaches to either a single target or to two potential targets. In the two target trials, two (out of the eight) differently colored targets (i.e., red and blue cues) were presented simultaneously,

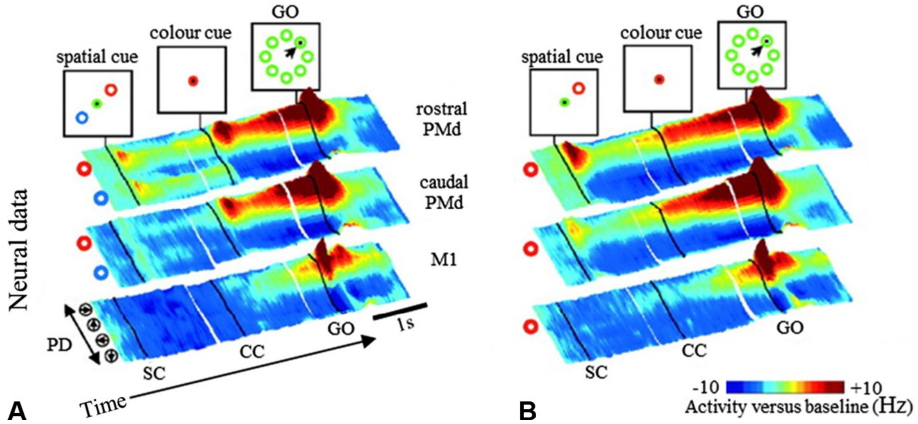

Fig. 8.4. Evidence that dorsal premotor (PMd) represents multiple potential actions long before a decision is made. *SC*, spatial cue; *CC*, color cue; *PD*, preferred directions. (**A**) Neuronal population activity with respect to the baseline in PMd and M1 in a reach choice task. Neurons were sorted by the preferred direction along the left edge. The top panels depict the stimuli presented to the animals at different epochs during the trial. Note that, during the delay period, when the animals were not aware of the actual goal location, the population encodes the two potential goal directions in PMd. M1 is not active during this period. (**B**) Similar to panel A but for single-target trials. Note that the PMd activity was weaker in trials with goal ambiguity than in trials in which the actual goal location was known during the delay period, suggesting that the two neuronal populations compete through inhibitory interactions to win the action competition. (Data from Cisek and Kalaska, 2005.)

each of which could be either a goal or a distractor (Fig. 8.4A). After a delay period, a color nonspatial cue (i.e., red or blue), presented in the center of the screen, indicated to the monkey the actual goal location. Interestingly, two neuronal populations selective for the two potential goals arose in PMd during the delay period (stronger effect in the rostral part of PMd than in the caudal part). After the color cue onset, the activity of the nonselected goal was reduced to the baseline. Note the lack of activity in M1 during the spatial cue (SC) and the color cue (CC) epochs. Only after the go-signal, M1 activity increased to generate the reach movement towards the target location. Importantly, the activity of the two neuronal populations in PMd was weaker in two-target trials than in the single-target trials (Fig. 8.4B), suggesting that the two groups of cells exert inhibitory influence on each other. This is consistent with the central axiom in parallel theory, according to which action selection emerges via inhibitory interactions (i.e., competition) within the regions that plan and guide action execution.

Similarly, Cui and Andersen (2007) studied whether reach and saccade actions are planned in parallel and before selecting one of them to execute. To address this question, they designed an effector-choice task in which monkeys autonomously chose between saccade and reach movements to the same visual cue (Fig. 8.5A), while neural activity was recorded from the parietal reach region (PRR) and the lateral intraparietal area (LIP). PRR and LIP are two PPC areas located on the medial and lateral banks, respectively, of the intraparietal sulcus, and are specialized in planning of reach and saccade movements, respectively.

Each trial started with the animals fixating both hand and eyes at the center of the screen. Next, a cue composed of adjacent red and green parts was presented in the periphery of the visual field. In the effector-choice trials, the cue extinguished and the animals had to wait for the go-signal (i.e., the extinguishing of the fixation point), and then decide to make either a reach or a saccade to the memorized location of the cue. The effector-choice trials were interleaved with effector-instructed trials in which the animals were instructed to make either a saccade or a reach by extinguishing only one of the colored components of the cue (e.g., if the red part was extinguished, the animal had to perform a reach to the memorized location of the target, and vice versa). Consistent with the theory of parallel preparation of motor actions, the activity increases in both LIP and PRR during the "cue-on" period, in which the animals did not know whether it was a decision or instruction trial. After the cue offset (i.e., extinguishing of the target), the animals knew that they were free to choose between reach and saccade, but they had to wait for the go-signal. During this delay, the activity separated in LIP and PRR, with LIP cells differentially more active when the animals chose to saccade (Fig. 8.5B) and PRR cells differentially more active when the animals chose to reach (Fig. 8.5C).

The theory that decision and action are coupled and tightly integrated has also received apparent support from neurophysiologic data showing decision-related activity in cortical regions that have traditionally been related to sensorimotor processing and action planning, such as premotor and parietal regions (Platt and Glimcher, 1999; Gold and Shadlen, 2000, 2007; Dorris

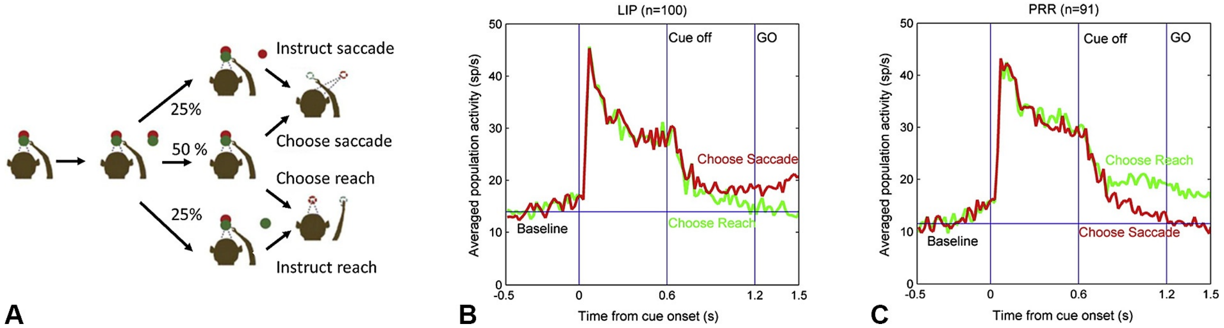

Fig. 8.5. Evidence that posterior parietal cortex (PPC) plans in parallel reach and saccade movements in an effector choice task. (**A**) The behavioral paradigm interleaved effector-instructed saccade (top) and reach (bottom) with effector choice (saccade or reach) trials (middle). (**B**) Averaged population activity (sp/s) across all isolated lateral intraparietal area (LIP) neurons ($n = 100$) during trials in which the animal chose saccade (red) instead of reach (green). The vertical blue lines indicate cue on, cue off, and go-signal, respectively. The horizontal blue line indicates the baseline activity. (**C**) Similar to panel B, but for parietal reach region (PRR) neurons ($n = 91$). Note that, at the cue onset, the activity increased in both LIP and PRR, because the animals did not know if this was a choice or instructed trial. This indicates that both LIP and PRR prepare in parallel saccade and reach actions to the target location. After the cue was extinguished, the animals knew that they were free to choose either effector, but they had to wait for the go-signal. During this delay period, the activity separated in LIP and PRR. The post-go activity of the LIP populations was higher than the baseline when the monkey chose saccade, but it dropped to the baseline if the animal selected reach. Similarly, the PRR activity was higher after the go-signal if the reach was chosen, but it dropped to the baseline if a saccade was selected. (Data from Cui and Andersen, 2007.)

and Glimcher, 2004; Sugrue et al., 2004). For instance, Platt and Glimcher (1999) recorded neural activity from the LIP while monkeys performed economic choice tasks. The animals were presented with two saccade targets, each of which was associated with a fluid reward. The two alternative choices varied in size or probability that the reward would be received, in a block of trials. The results showed that the activity of the LIP neurons represents specific eye movements to the targets, and is modulated by the reward magnitude and the probability that the eye movement will result in a reward (Platt and Glimcher, 1999). Similar findings have also been reported in other cortical and subcortical regions, such as PMd (Pastor-Bernier and Cisek, 2011) and superior colliculus (Thevarajah et al., 2009).

Behavioral studies have also explored the mechanisms of action selection, providing evidence that motor decisions involve the parallel specification of multiple potential actions prior to choosing one of them to execute. For instance, reaching experiments showed that when individuals are presented with multiple potential targets and forced to initiate a rapid reach before one of them is cued for action, reaches often launch to a spatially averaged location between the targets. After the cue onset, the reaches are corrected in flight to the actual goal location (Fig. 8.6) (Hudson et al., 2007; Chapman et al., 2010; Gallivan et al., 2011).

Similar behavior has also been reported in rapid eye movements, when humans or animals are presented with multiple saccade targets or a target surrounded by similar distractors (Chou et al., 1999; Findlay and Walker, 1999; McSorley et al., 2006). This behavior, which has been termed “global effect” or “spatial averaging,” has been interpreted as evidence of motor averaging – i.e., the brain prepares in parallel multiple competing single-target actions and executes a weighted average of them.

Even though these observations are consistent with the parallel theory in decision making, they can also be interpreted within the sequential theory. In particular, it could be argued that the neural representation in the sensorimotor and premotor regions is not “genuinely” motor, but instead it is related to the sensory properties of the targets, such as their visual location and orientation (Padoa-Schioppa, 2011). Similarly, the spatial averaging behavior in reach and saccade choices could reflect visual averaging – i.e., planning of a single action towards an averaged visual-spatial target location – rather than motor averaging (Gallivan et al., 2015).

Probing the decision-making circuitry using reversible pharmacologic inactivation: an animal model for extinction

All of these findings have created considerable uncertainty as to whether decision and action can involve two separate processes or only a single process. One approach to dissociate these two hypotheses is to temporarily inactivate particular brain regions and observe the effects on decision making. Reversible pharmacologic inactivation has proved to be an efficient method to complement lesion experiments in a variety of research

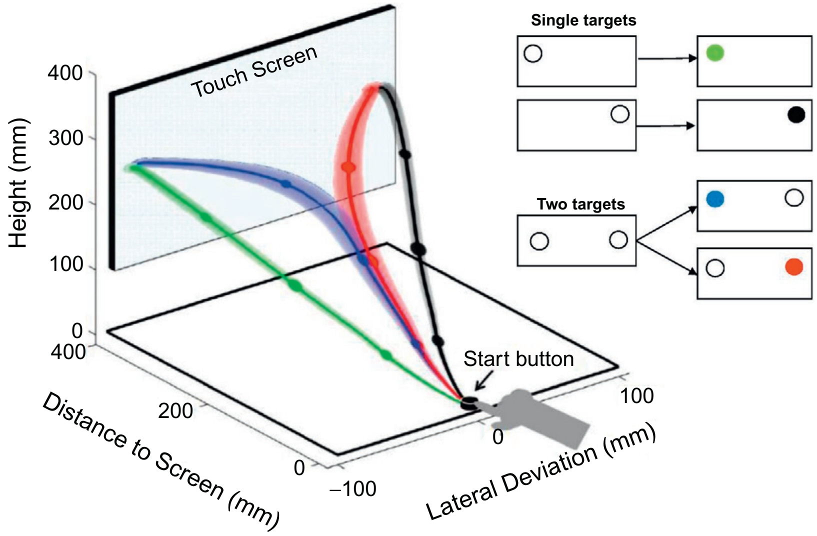

Fig. 8.6. Experimental setup with the averaged reach trajectories during a rapid-reach task (Chapman et al., 2010). Two potential targets were presented simultaneously in each visual field: one was cued as the target after the movement initiation. Reach trajectories were initially aimed towards an intermediary location before they were corrected in flight to the target location (blue and red traces). This "spatial averaging behavior" has been interpreted as evidence of motor averaging, i.e., people simultaneously prepared two motor plans before deciding between them, but did not always completely suppress the unselected motor plan before initiating a movement. The two-target trials were interleaved with control trials in which a single target was presented in the left or the right visual field. In this case, there was no uncertainty about the location of the goal and reaches were launched directly to the target location (green and black traces). (Data from Chapman et al., 2010.)

studies, including sensorimotor control and decision making. Muscimol or other gamma-aminobutyric acid ($GABA_A$) agonists are typically used to inactivate brain areas, because they do not affect fibers of passage, simplifying the interpretation of what neural substrate is affected. The main advantage over lesion studies is that it can be performed in the same subject both in control (no drug injection) and "lesioned" states, since the drug action is limited to a few hours (Hupe et al., 1999).

Recent studies explored the effects of cortical and subcortical inactivation in oculomotor tasks. In one of these studies, monkeys were trained to perform three tasks: (1) saccades to a single target; (2) saccades to synchronous and asynchronous bilateral targets; and (3) visual search of a target in the presence of similar distractors (Wardak et al., 2002). LIP inactivation did not affect the eye movements to the single targets. However, it reduced significantly the contralesional choices in the presence of bilateral targets, and increased substantially the search time for a contralesional target in the visual search task. The inactivation of the superior colliculus in visual search tasks also caused reduction of saccades (McPeek and Keller, 2004) and reaches (Song et al., 2011) to the targets located in the affected zone.

A study in our lab explored the effects of LIP inactivation in functional reorganization of the brain network involved in saccade choices (Wilke et al., 2012). In particular, Wilke et al., inactivated LIP (Fig. 8.7A), while measuring functional magnetic resonance imaging (fMRI) activity during memory-guided choices between two bilateral saccade targets (free-choice trials). Free-choice trials were interleaved with instructed trials, in which a single target was presented either in the left or the right visual field.

LIP inactivation did not impair the ability of the animals to perform saccades to instructed single targets in either hemifield (Fig. 8.7B). However, it caused a strong choice bias to ipsilesional targets when two targets were presented simultaneously in the opposite hemifields (Fig. 8.7C). This spatial choice bias is reminiscent of the extinction symptoms observed in human patients with parietal lesions, as previously summarized. At the neural activity level, LIP inactivation caused a reduction of activity in the upper bank of the superior temporal sulcus (temporal parietal occipital area) during the single-target trials, especially in the lesioned hemisphere. Interestingly, the activity was enhanced in both hemispheres in the (infrequent) two-target trials in which the animals selected the contralesional target.

This finding only partially agrees with interhemispheric competition models of spatial neglect/extinction (Kinsbourne, 1977), which would predict an increase in the lesioned hemisphere and a decrease in the undamaged hemisphere. Rather, it suggests an additional component of interhemispheric cooperation in the compensation of extinction deficits. One possibility is that

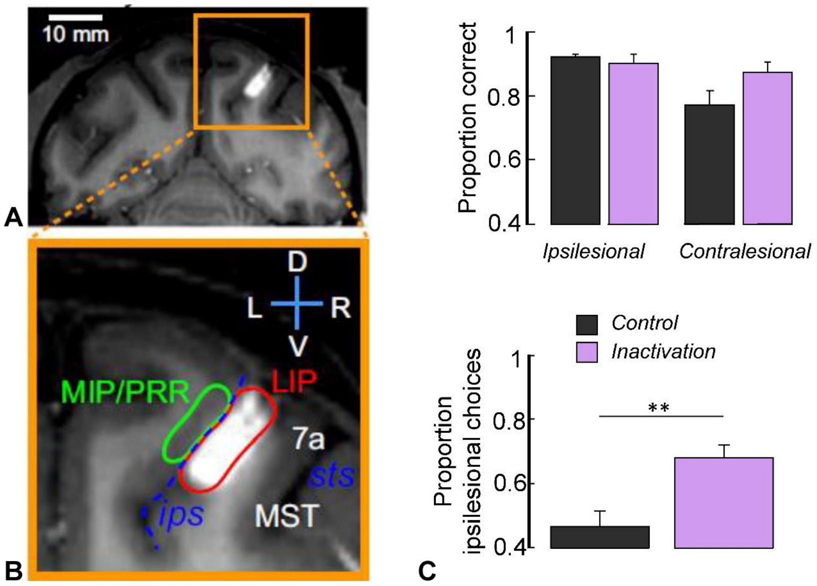

Fig. 8.7. Lateral intraparietal area (LIP) inactivation sites and behavioral effects in an oculomotor choice task (Wilke et al., 2012). (**A**) Coronal T1-weighted magnetic resonance (MR) sections visualizing the right-hemisphere injection sites with the gadolinium MR contrast agent (white area) (bottom panel depicts a magnified view of the inactivation area) *ips*, intraparietal sulcus; *MIP*, media intraparietal area; *MST*, medial superior temporal region; *PRR*, parietal reach region; *sts*, superior temporal sulcus. (**B**) Proportion of correct saccades to ipsilesional and contralesional targets before (black) and after (purple) inactivation. Note that inactivation did not impair the saccade performance to either hemifield. (**C**) Proportion of ipsilesional choices before and after inactivation. Note the significant increase of ipsilesional choices after LIP inactivation. Error bars indicate SEM; ** $p < 0.01$. (Data from Wilke et al., 2012.)

LIP inactivation causes an overall increase in effort that affects both hemispheres. Consistent with this hypothesis, recent studies showed that the choice bias after LIP inactivation is alleviated by increasing the amount of reward associated with the contralesional hemifield (Balan and Gottlieb, 2009). Similar findings were also reported in oculomotor decisions after pulvinar inactivation – i.e., ipsilesional choice bias is alleviated by increasing the reward to contralesional targets (Wilke et al., 2013).

All of these studies suggest that cortical and subcortical regions, such as LIP, superior colliculus, and pulvinar, are within a network for making saccade decisions. It is likely that the inactivation of these regions increases the action cost (i.e., effort) required to implement the choice, or decreases the expected reward in the contralesional hemisphere (i.e., devaluation), resulting in extinction-like symptoms. However, it could be argued that the choice bias after inactivation is due to an attentional deficit, rather than a deficit in the decision process. To dissociate between these two hypotheses, we need to study whether extinction is effector-specific.

Recently, our lab addressed this question by inactivating PRR (Fig. 8.8A) while monkeys performed memory-guided reach and saccade choices to bilateral targets (free choices) (Christopoulos et al., 2015b). Free-choice trials were interleaved with instructed (single-target) trials. Reaches were performed using a two-dimensional joystick positioned between the legs of the animals. Animals used the arm opposite to the inactivated hemisphere in the reach movements. PRR inactivation did not impair reach movements to single targets presented in either hemifield (Fig. 8.8B). However, it led to a strong reduction of contralesional choices, but only for reaches (Fig. 8.8C). Saccade choices were not affected (Fig. 8.8D). Therefore, PRR inactivation affected only the reach choice preference, leaving the sensory, memory, and motor components of the task largely intact. These results cannot be explained as an effector-nonspecific deficit in spatial attention or awareness, since the “lesion” had an impact only on reach and not on saccade choices.

Our findings complement the results from another recent inactivation study in monkeys, showing that LIP and PRR are also causally involved in perceptual decisions (Kubanek et al., 2015). This study used a double-target paradigm in the context of a stimulus onset asynchrony task with variable delay between the onsets of the two targets. The goal was to identify which target appears earlier. LIP inactivation biased only the saccade choices, whereas the PRR inactivation biased only the reach choices.

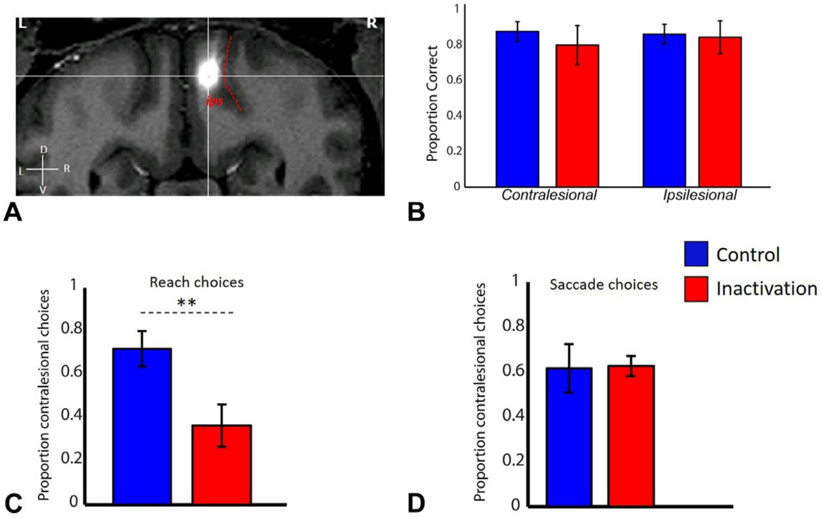

Fig. 8.8. PRR inactivation sites and behavioral effects in reach and oculomotor choice tasks. (**A**) Coronal T1-weighted magnetic resonance (MR) section visualizing one of the injection sites with the gadolinium MR contrast agent (white area). (**B**) Proportion of correct reaches to single ipsilesional and contralesional targets before (blue) and after (red) inactivation. No effects on parietal reach region (PRR) inactivation of reach performance. (**C**) Proportion of contralesional reach choices between two targets before and after inactivation. Note that inactivation led to a strong reduction of contralesional reach choices. (**D**) Proportion of contralesional saccade choices before and after inactivation. In contrast to reach choices, PRR inactivation did not affect saccade choices. These findings suggest that PRR is part of a network for making reach decisions. Error bars indicate SEM; ** $p < 0.01$. (Data from Christopoulos et al., 2015b.)

Overall, the effector-specific organization of PPC in motor decisions provides a new conceptual way to understand the pathophysiology of extinction. Instead of viewing extinction as just a selective attention deficit, it can be viewed alternatively, or additionally, as a deficit in the decision-making process. The current evidence suggests that PPC encodes information related to the decision-making process. Therefore, it is likely that parietal damage influences the value representation of the available options. For instance, parietal lesions may lead to devaluation of the contralesional hemifield and/or increase of the effort to perform actions to the contralesional hemifield, making ipsilesional targets more desirable. Further experimental work is required to validate this hypothesis.

A computational perspective of extinction

We have recently developed a computational framework to model the behavioral and neural mechanisms of motor decisions (Christopoulos et al., 2015a). It consists of a set of dynamic neural fields, each of which simulates the neural processes of spatial attention, expected reward, action cost, motor preparation, and decision making within a population of 181 neurons (Fig. 8.9). Each neuron has a preferred direction between 0 and 180°. The reach and saccade fields are the two motor preparatory nodes of the network that can be equated to PRR and LIP, respectively. Information about the location of the targets and the expected outcome (e.g., reward, selection bias) to move towards particular directions is encoded by the spatial sensory input field, and the goods value field, respectively. The output of these fields sends excitatory projections (green arrows) to the reach and saccade field in a topologic manner – i.e., each neuron in one field drives the activation of the corresponding neuron in the field to which it projects. The effort required to reach/saccade toward a particular direction is encoded by the action cost field. The output of this field is projected to the reach and saccade fields through one-to-one inhibitory connections (red arrows) to penalize costly motor actions. Hence, the role of the reach and saccade fields is twofold: (1) prepare the reach and saccade movements; and (2) integrate information from disparate sources to evaluate the alternative choices. The normalized activity of the motor preparatory fields encodes the relative desirability of moving to a particular direction with respect to the alternative options.

Consider now the PRR inactivation experiment with reach and eye choices presented in Christopoulos et al. (2015b). When two reach targets are presented simultaneously in the opposite visual fields, the activity of two neuronal populations selective for these two targets increases in the reach field. The decision emerges via inhibitory interactions (i.e., competition) within the neurons in the reach field. A reach decision is made once the activity of one of the neuronal populations exceeds a predefined threshold (blue discontinuous line) in the reach

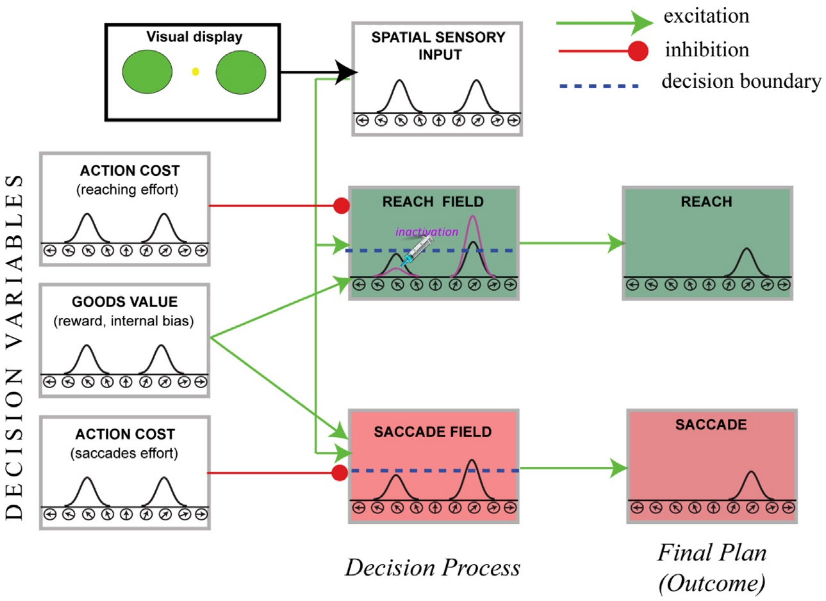

Fig. 8.9. A simplified version of the neurodynamic framework developed to model the computational instantiation of motor decisions (for more details, see Christopoulos et al., 2015a). We modeled the parietal reach region (PRR) inactivation experiment described in Christopoulos et al. (2015b) within this framework to provide new conceptual advances in understanding the mechanisms underlying extinction. According to this model, PRR and lateral intraparietal area encode the relative desirability of reach and saccade choices (black bell shape), respectively. Muscimol injection in PRR influences the desirability values of the reach choices (purple bell shapes), shifting the choice bias to ipsilesional targets.

field. In the control sessions, both targets provide the same expected reward and are located about the same distance from the starting position of the joystick cursor. Hence, both options have about the same desirability value, unless the animals have an internal bias to select one option over the other, as observed in our inactivation experiments (Christopoulos et al., 2015b). However, in the inactivation sessions, the muscimol injection inhibits the activity of one of the neuronal populations, reducing the relative desirability of the corresponding target (purple bell shape) and consequently the choice bias is shifted to the alternative option. All other components of the task (i.e., sensory, memory, and motor) remain largely intact. Additionally, the neuronal activity in the saccade fields is not affected by the drug injection, and hence there is no effect on saccade choices. The computational framework predicts similar findings for LIP inactivation experiments – i.e., reduction of contralesional choices, but only for saccades.

According to the model, the choice bias can be alleviated by either modulating the activity of the intact neuronal population (e.g., through brain stimulation), or by modulating decision-related factors such as the expected reward and the action cost. For instance, by increasing the expected reward of the target located in the lesioned hemisphere, or decreasing the effort required to reach to that target, we expect to restore the choice preference to the control level (i.e., prior to inactivation). The next section presents more detailed rehabilitation methods and treatments to accelerate recovery from extinction symptoms.

NEURAL RESTORATION

Possible rehabilitation strategies for extinction using a decision-making framework

The NHP model of extinction points to two profound concepts of its origin that can guide the design of therapeutic strategies. The first is that extinction, in part, is a result of biasing decision making. The second is that, although extinction produced by a lesion to one hemisphere brings about a contralateral field deficit, the changes in cortical activity are bilateral and encompass the functioning of both hemispheres.

As mentioned earlier, with pulvinar inactivations animals are still aware of the stimuli in the affected field, but are biased against choosing these stimuli as targets for action (Wilke et al., 2013). This bias can be reduced by increasing the expected reward for choosing the contralateral target. Thus, the competition is not at the level of stimuli entering awareness, but rather at the level of decision making. Expected value computations include both reward and cost components. It is possible that lesions result in greater cognitive effort in choosing targets in the contralateral hemispace.

Therapies for extinction and neglect have included using prisms to bias behaviors toward the contralesional space by displacing the retinal image (Rossetti et al., 1998). Another proposed therapy is to increase the attentional salience of targets in the contralesional space since neglect is reduced by increasing the salience of stimuli in the affected hemifield (Bays et al., 2010). However, increasing salience by increasing contrast in the contralateral hemifield in NHPs with pulvinar inactivation was not nearly as effective as increasing the expected reward for actions in the contralesional space (Wilke et al., 2013). Thus, training paradigms like those for testing extinction, and which manipulate the expected reward, may be useful to recalibrate competitive choice mechanisms between hemifields.

The animal studies documenting changes in cortical activity with PPC inactivations and extinction suggest possible invasive therapies for ameliorating extinction and neglect. These studies show that a simple model of biased competition between hemispheres does not explain extinction (Wilke et al., 2012). Inactivation of LIP in one hemisphere produces an overall reduction of activity in many areas in both hemispheres. When the animals still selected stimuli in the affected hemifield, activity in the two hemispheres was both enhanced and balanced.

It could be imagined that chronic brain stimulation, similar to deep-brain stimulation used for movement disorders, could be used for treating extinction and neglect. However, the NHP data suggest that bilateral cortical stimulation may be the most beneficial, as extinction is relieved when activity in both hemispheres is boosted. Another possible target for patients with PPC lesions would be the pulvinar, which has access to much of the dorsal sensorimotor areas that may be spared from lesions. Stimulation of the pulvinar on the lesion side may be effective in also restoring activity to the healthy hemisphere. Unilateral pulvinar inactivation produces very pronounced reduction in activity in the contralateral hemisphere, suggesting that unilateral pulvinar stimulation may enhance activity in both hemispheres and restore balance between them (Wilke et al., 2012). Bilateral pulvinar stimulation may be even more effective than unilateral stimulation, or may be necessary if unilateral stimulation is not effective.

Neural prosthetics based on superior parietal lobule activity

The last section discussed possible therapies to restore function after PPC lesions. However, using neural signals recorded from PPC can be harnessed to help patients with lesions to other parts of the brain through neural prosthetics.

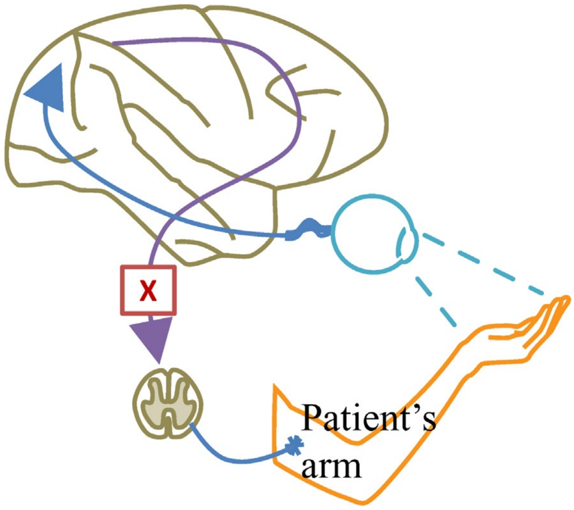

Fig. 8.10. Schematic of the interruption of movement commands for visually guided reaching with spinal cord injury.

Studies using BMI technology have promise in assisting paralyzed patients to use assistive devices such as robotics and computers. A good example of this application is to assist tetraplegic subjects, although similar approaches can be designed for stroke and degenerative brain diseases. In a tetraplegic subject, the connections between the commands for movement have been broken due to spinal cord injury (Fig. 8.10). However, the majority of the pathway for visually guided motor behaviors remains intact. One source of control signals for neuroprosthetics is the motor cortex and has been used successfully for the control of a robotic limb for activities of daily living and computer cursors for communication (Hochberg et al., 2006, 2012; Collinger et al., 2013; Gilja et al., 2015).

Our lab has explored using the PPC as a source of signals for BMIs. In NHPs, we found excellent control of trajectories for cursor movements, similar to motor cortex, and uniquely for indicating the intended goals of a movement (Musallam et al., 2004; Mulliken et al., 2008a). We have recently extended this research to human tetraplegics by implanting the PPC with arrays of electrodes in the presumed equivalent of the anterior intraparietal area and Brodmann area 5 (Aflalo et al., 2015; Klaes et al., 2015a). In NHPs these areas show a specialization for grasping and reaching and were targeted in our human subjects by asking them to imagine grasping and reaching and recording the corresponding changes in blood flow using fMRI.

The human studies were guided by the concept that PPC represents a more "cognitive" area for motor control, and as such represents the general intent of the subject (Andersen et al., 2010). From NHP studies we knew that complementary signals to motor cortex pertinent to BMI

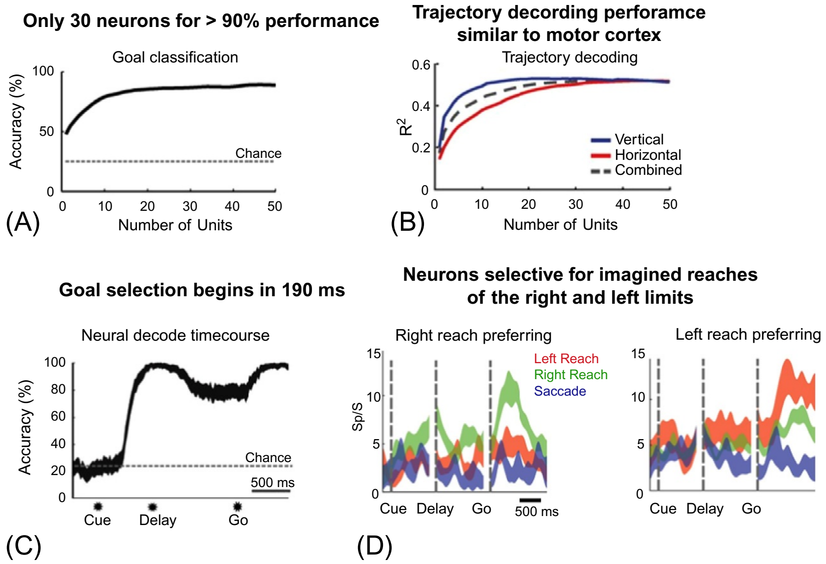

Fig. 8.11. Neural recordings from posterior parietal cortex of a human tetraplegic showing: (**A**) goal decoding; (**B**) timing of goal decoding; (**C**) trajectory decoding; and (**D**) neurons selective for the right and left limb imagined reaches. (From Aflalo T, Kellis S, Klaes C, et al. (2015) Decoding motor imagery from the posterior parietal cortex of a tetraplegic human. Science 348: 906–910 with permission from AAAS.)

applications included the coding of the goals of movements (Snyder et al., 1997). The use of goal signals resulted in very fast determination of the targets of a movement and could also augment decoding when combined with trajectory signals (Musallam et al., 2004; Mulliken et al., 2008a). The PPC was also found to have trajectory signals that could be decoded at a similar accuracy to motor cortex (Hauschild et al., 2012). The PPC trajectory signals peaked at around 0 ms latency with respect to the ongoing direction of movement, later than the M1 activity which precedes the movement (Mulliken et al., 2008b). This and other observations led us to propose that the trajectory signal in PPC represents an estimate of the current state of the limb, consistent with ideas of optimal control for error correction, and also for predicting the sensory consequences of a planned movement. Other potentially unique signals from PPC were suggested by NHP studies, and include bilateral representation of reaches, selectivity for hand shape during grasping, and the encoding of sequences of movements (Murata et al., 2000; Baldauf et al., 2008; Chang et al., 2008).

The NHP findings were borne out by our human studies (Aflalo et al., 2015). The human PPC can accurately code the goal for an imagined reach with fewer than 30 neurons (Fig. 8.11A) in under 200 ms (Fig. 8.11B). The trajectories of imagined reaches were read out with similar accuracy to that recorded in motor cortex (Fig. 8.11C). The PPC represents reaches with either limb, with some neurons coding imagined reach of either the right or left limb (Fig. 8.11D) and many for reach with either limb.

The anterior intraparietal area in monkeys has been found to encode the visual images of objects as well as the hand configuration for grasping them (Murata et al., 2000). We found with our human anterior intraparietal area recordings that this was also true for humans (Klaes et al., 2015a) (Fig. 8.12). Beyond that we found that imagined hand shapes could be imagined that did not indicate the hand shape for grasping the visual cue. This result indicates that the anterior intraparietal area is very flexible in terms of coding hand gestures. Such flexible and cognitive control of hand gestures would be useful for communication.

The studies in humans also expanded greatly our findings regarding the neurophysiology of the PPC and thus provides the scientific foundations for further neuroprosthetic development using the PPC. We found that the representation of intended body movements in the PPC, within a single 4 × 4 mm of cortex covered by the electrode array, includes much of the body (Zhang et al., 2015). Body movements for the hands, arms, and shoulders on both sides of the body are represented. Moreover, even cells selective for speech were found. However, there is also a highly structured organization of this information. Neurons respond to a limited number of the potential variables and generally show effector-specificity. For instance, a neuron may respond to right and left imagined squeezing of the hand but not moving the arm, shoulder, or speech. The cognitive contexts of imagining versus attempting movements also showed extensive, but not complete, overlap. The representations of the different variables were independent across the

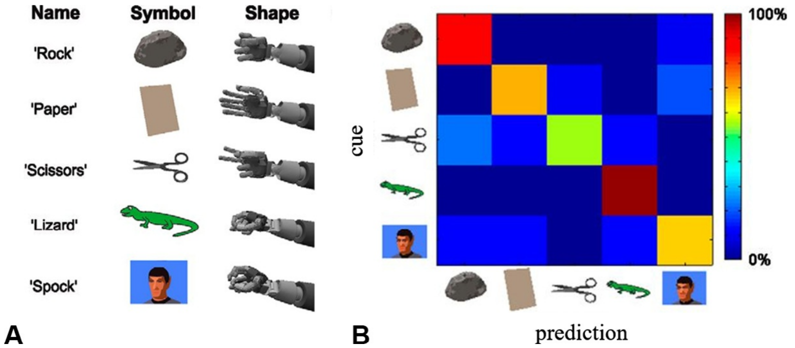

Fig. 8.12. (**A**) The subject was shown different symbols, borrowed from the rock–paper–scissors–lizard–Spock game, and asked to imagine the hand shapes (illustrated by the robotic hand shapes that were used in some of these experiments). (**B**) The decoding of the imagined hand shapes that were cued by the five images. Note that many of these hand shapes are distinct from the affordances of the instructing stimulus, namely, except for the rock, the hand shapes are not directly related to the shape of the hand that would be required to grasp the cue. (From Klaes C, Kellis S, Aflalo T, et al. (2015a) Hand shape representations in the human posterior parietal cortex. J Neurosci 35: 15466–15476 with permission from the Journal of Neuroscience.)

population, and as a result all of the variables can be decoded. The distributed but decodable nature of the PPC representation has an amazing advantage for BMI applications, since it implies that a single implant can be used to decode many intended movements of different body parts. It is currently not known if the motor cortex has a similar diversity of responses within a patch of cortex.

Another finding, particularly pertinent to extinction, is that the PPC encodes movement decisions (Klaes et al., 2015b). It also encodes quantities and mathematic operations, perhaps taking advantage of its action-based machinery, which includes representing space, making coordinate transformations between spatial representations, and encoding the dynamics of actions (Kellis et al., 2015).

CONCLUSIONS

Extinction is a common neurologic deficit that often occurs as one of a constellation of symptoms seen with lesions of the PPC. Although extinction has typically been considered a deficit in the allocation of attention, new findings, particularly from NHP studies, point to one potential and important source of extinction as damage to decision-making circuits for actions within the PPC. This new understanding provides clues to potential therapies for extinction. Also the finding that the PPC is important for action decisions and action planning has led to new neuroprosthetic applications using PPC recordings as control signals to assist paralyzed patients. Damage to the action apparatus in PPC causes extinction; on the other hand, decoding from a functioning PPC can provide the action signals for controlling BMIs.

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