Chapter 14

On the difficulties of integrating evidence from fMRI and electrophysiology in cognitive neuroscience

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Abstract

Functional magnetic resonance imaging (fMRI) and single unit physiology are two of the most widely-used methods in cognitive neuroscience and neuroeconomics. Despite the fact that practitioners of both methods share a common goal—understanding the mechanisms underlying behavior and cognition—their efforts are rarely directly linked. Here we consider some of the reasons for apparent discrepancies between findings of fMRI and electrophysiological studies. We examine these problems through the lens of two case studies—decision-making under uncertainty and fictive learning—derived from our own research program. Despite this narrow focus, these arguments are likely to extend to other areas of study. We find that major differences in the neural events measured by the two methods, the behavioral techniques employed with animal and human subjects, and the intellectual history and unique culture of each discipline, contribute to difficulties in providing a wholly synthetic account of the mechanisms underlying cognition and decision-making. These observations endorse more collaborative efforts conducting parallel research using analogous, if not identical, behavioral techniques using both brain imaging and single unit physiology.

14.1 Introduction

Neuroimaging in general, and fMRI in particular, have revolutionized cognitive neuroscience (Huettel et al., 2008; Logothetis and Wandell, 2004; Ogawa et al., 1990) and use of these techniques now permeates diverse fields, including psychology, neuroscience, and economics, and has begun to influence sociology, law, philosophy, anthropology, and other related fields. The popularity of neuroimaging springs both from its wide availability
Prima facie, single-unit physiology and functional neuroimaging should be highly complementary techniques. Scientists who use the two methods are generally interested in the exact same problems and aim to provide a material answer to important questions in psychology, cognitive science, and philosophy (e.g., Greene et al., 2001), as well as economics (Camerer, 2008), political science (Amodio et al., 2007), sociology (Amodio et al., 2004; Harris and Fiske, 2006), and other fields. The need for communication between practitioners of these diverse methods is further motivated by the insight they can provide on debilitating diseases, including addiction, depression, autism, and other pathologies. Despite common interests and goals, however, there is a surprising disconnect between

![Fig. 14.1](https://example.com/fig14.1.png)

**Fig. 14.1** (A) Schematic of the inferred relationship between spiking activity and BOLD activity. BOLD activation (right) reflects a convolution of individual action potentials (left) with an idealized hemodynamic response function (center). (B) Single-unit physiology studies typically plot peristimulus time histograms, reflecting averaged responses of single units across multiple trials. These are then compared in different conditions, such as two attention conditions in the example data drawn from area V4. Single-unit responses typically last a few hundred milliseconds, and are characterized by a low baseline firing rate, a rapid transient response, followed by a longer lasting sustained response. This entire response typically lasts around 250–500 ms. (C) The idealized hemodynamic responses function is characterized by a very small initial dip, a large and relatively brisk enhancement, and a long, slow suppression, followed by a return to baseline. The entire process typically lasts about 15 s.

Reprinted from Hayden et al. (2008a) Posterior cingulate cortex mediates outcome-contingent allocation of behavior. Neuron, with permission from Elsevier.
INTRODUCTION

The data and interpretations issuing from imaging and neurophysiological studies (see, for example, Huk et al., 2001; Nir et al., 2007; Sirotin and Das, 2009; Yoshor et al., 2007).

The signal measured by fMRI depends on the relaxation times in the spin of hydrogen atoms that have been aligned by a large magnetic field (Huettel et al., 2008). The quantity most often measured by fMRI is known as the blood-oxygen-level-dependent change (BOLD). Specifically, fMRI measures changes in relaxation times due to changes in levels of deoxyhemoglobin in small units of brain volume referred to as voxels. Each voxel is typically about 3–4 mm on a side. An implicit assumption in many people’s minds is that the BOLD response is the outcome of a convolution between acute spiking activity and a canonical hemodynamic impulse response function (Fig. 14.1A) (Huettel et al., 2008; Logothetis and Wandell, 2004). Thus fMRI studies typically assume that BOLD activity reflects underlying neural events, and these events are inferred through a simple process of deconvolution.

Although developed much earlier than fMRI, single-unit physiology (which measures single-unit activity, SUA) remains a core method in cognitive neuroscience. The term “single unit” refers to the single neuron whose spiking responses are recorded by an electrode placed near to, but outside of, the cell membrane. The techniques necessary to record extracellular potentials from awake, behaving monkeys were developed by Ed Evarts (Evarts, 1966) at the NIH in the late 1960s, and had their antecedents in earlier research by Penfield, and in the anesthetized recordings made in the labs of Kuffler and others (Barlow et al., 1957; Penfield and Jasper, 1954). Originally used to study motor control (Evarts, 1968), sensory perception (Goldberg and Wurtz, 1972a; Mays and Sparks, 1980; Mountcastle et al., 1975), memory (Funahashi et al., 1989; Fuster and Alexander, 1971; Kubota and Niki, 1971), and attention (Goldberg and Wurtz, 1972b), processes studied by single-unit physiology quickly grew to include executive control (Hanes and Schall, 1996; Niki and Watanabe, 1979), face recognition (Gross et al., 1979), sensory (Shadlen and Newsome, 1996), and economic decision-making (Platt and Glimcher, 1999), among other cognitive processes. Other closely related techniques include local field potential (LFP) recording and multi-unit recording (MUA). In contrast to fMRI, these methods typically employ animal subjects (with some exceptions, see below), and thus require behavioral training, surgical support, and reliance on simple tasks. Single-unit physiology can be performed on awake, behaving monkeys, rats, mice, birds, and ferrets, among other animals.

Thus, BOLD and SUA measure distinct aspects of neural processing, in much the same way that different prismatic lenses image separate parts of the spectrum of visible light. Single-unit physiology measures spiking activity—predominantly generated by the cell bodies of large pyramidal neurons—and thus emphasizes outputs of local processing. Although less certain, BOLD appears to reflect a blend of high-frequency synchronized spiking, synaptic potentials in dendrites, and membrane oscillations—processes that reflect inputs, local computations, and outputs, albeit indirectly. We note that, at the present time, none of these physiological processes has privileged status in explaining the mechanisms underlying cognition.
Given these differences in measurement focus, it is difficult to draw a straight line connecting single-unit and fMRI studies, even when they address the same questions. In the following sections, we discuss this problem in a detailed fashion by examining two case studies of single-unit physiological experiments designed to tackle neuroeconomic questions that have also been explored with brain imaging. In addition to discussing the specific results of these studies, we also dwell on the thorny issues raised by these same physiological results for interpreting comparable BOLD data. Despite many fundamental differences between the two methods, we remain optimistic that additional work, both empirical and sociological, can help bridge these gaps and lead to greater understanding of the neural basis of cognition.

14.1.1 Case study 1: spiking activity and decision-making under uncertainty

Decision-making under uncertainty is an economic problem that has received scrutiny from both physiologists (Barraclough et al., 2004; Fiorillo et al., 2003; Hayden et al., 2008a; McCoy and Platt, 2005) and neuroimagers (Daw et al., 2006; Hsu et al., 2005; Kuhnlen and Knutson, 2005; Weber and Huettel, 2008), as well as from economists (Samuelson, 1963; Von Neumann and Morgenstern, 1944), psychologists (Heilbronner et al., 2008; Kacelnik and Bateson, 1996) and theorists (Yu and Dayan, 2005).

Several recent neuroimaging studies in human subjects reported distinct foci of activation associated with risk and uncertainty, and making decisions in volatile environments, including posterior and anterior cingulate cortices, dorsal and ventral striatum, orbito-frontal cortex, and lateral prefrontal cortex (for reviews, see: Platt and Huettel, 2008; Rushworth and Behrens, 2008). To understand these processes at the neuronal level, we first probed the spiking activity of single neurons in monkeys making simple decisions between probabilistic and deterministic fluid rewards (Fig. 14.2a; Hayden and Platt, 2007, 2008; Hayden et al., 2008a, 2008b). On each trial, monkeys chose between two options of equal expected value (typically 200 microliters of an immediate fruit juice reward), but differing in the variability, and thus economic risk, of the potential outcomes. The variance in reward payout of the risky option was adjusted randomly every 50 trials, while the safe option was fixed at an intermediate value. Monkeys preferred the risky option in this task, and preference increased with increasing variance in reward. Moreover, local patterns of choice strongly depended on the recent history of rewards and choices (Hayden et al. 2008).

To understand the neuronal mechanisms underlying this behavior, we began by recording spiking activity of neurons in the posterior cingulate cortex (CGp). CGp is a large brain region located in a belt around the corpus colosum, lying posterior to the central sulcus and likely to be homologous to the human posterior cingulate cortex (Hayden and Platt, 2009a; Vincent et al., 2007; Vogt et al., 1992, 1993). CGp is strongly and reciprocally interconnected with the anterior cingulate cortex, medial temporal lobe, and hippocampus, as well the parietal lobe, and is therefore well-positioned to integrate information about action, reward, and risk and guide choice (Hayden et al., 2008).
We found that tonic firing rates of single CGp neurons systematically varied with the variance in reward associated with the risky option (McCoy and Platt, 2005). Spiking activity also predicted whether the risky option would be subsequently chosen (McCoy and Platt, 2005). We also found that firing rates changed following reward delivery, signaling the size of the reward obtained from a risky option and predicting subsequent changes in choice behavior (Hayden and Platt, 2009a). When rewards are deterministic,

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**Fig. 14.2** Neuronal spiking and risky decision-making. (A) Schematic of task used to study risky behavior in monkey (McCoy and Platt, 2005; Hayden et al., 2008a). First, small fixation square appears centrally. Once fixation is acquired and maintained for one second, two eccentric targets appear to the left and right of the central fixation square. Central square is then extinguished, signaling that a saccade to one of the targets is required. Following saccade, reward is given. (B) Likelihood that monkey will switch from risky to safe target or vice versa from one trial to the next depends on the outcome of the trial. Switching likelihood is greater following smaller than expected outcomes than following large outcomes. Likelihood is about even following safe choices. (C) Plot of average firing rate of all CGp neurons in population following large and small outcomes of gambles, as well as following safe choices. Firing rates of all neurons during a 500 ms epoch after saccades is closely aligned with the likelihood of switching. (D) Plot of the distribution of firing rate changes associated with large and small outcomes of gambles. The distribution of response properties within CGp is highly heterogeneous (panels B–D based on Hayden et al., 2008a). Black regions indicate neurons with significant modulations (p<0.05); white regions indicate neurons with non-significant modulations.

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CGp neurons encode reward value monotonically (McCoy et al., 2003), but when rewards are uncertain CGp neurons signal reward size with respect to the best obtainable reward, i.e., ditonically (Hayden and Platt, 2009a). This pattern of spiking also predicted the likelihood that the animal would adjust his behavior (Fig. 14.2B–D), suggesting that CGp contributes to risky decision-making by signaling the need to change behavioral strategies (see also Pearson et al., in press). These results clearly and unequivocally implicate CGp in the representation of variables that contribute to risky decision-making.

It remains unclear whether neuroimaging studies would replicate these results. Most importantly, we observed consistent heterogeneity of modulation in spiking activity across the population of studied neurons. Approximately half the neurons in our sample showed elevated spiking activity following larger than expected rewards, and about half showed significantly decreased spiking following such outcomes. Although we did detect a statistically significant preponderance of neurons with larger firing-rate changes to smaller outcomes, the bias was not overwhelming, and a substantial minority of neurons showed stronger spiking activity for better-than-expected outcomes. This heterogeneity may reflect the existence of two fundamentally distinct classes of neuronal spiking responses, with two different outputs that happen to be intercalated. Alternatively, these two types of neurons may converge on a single output structure, where they are gated in a non-linear competition (Gold and Shadlen, 2002; Lee et al., 1999; Salzman and Newsome, 1994). Heterogeneity in neuronal spiking responses appears to be quite common in cortical areas in particular (see Table 14.1 for a partial list of examples).

Unlike single-unit spiking, BOLD measures aggregate neuronal processing in a given brain region and is thus blind to anything other than the mass action effects within a given voxel. Consequently, the BOLD signal fails to capture diversity in the functional properties of different categories of neurons in a given voxel—at least given current spatial sensitivity. To our knowledge, very little empirical work has investigated how the BOLD signal varies with the activity of heterogeneous populations of neurons with excitation and suppression of spiking. It thus remains unclear how BOLD signal in CGp would vary in this task. In the worst case, the BOLD signal would not distinguish between enhanced and suppressed spiking, leading to false negative results. Alternatively, the BOLD signal may reflect slight variations in the balance between excitation and suppression.

Another closely related problem is that many neurophysiological studies report the presence of neurons with significant effects—even if the percentages are a small proportion of all neurons in the area. In this case, it is possible that BOLD activation would be too weak to reach significance. In general, we know very little about the mapping between the proportion of neurons activated in a study and the expected BOLD signal.

Thus, it is not hard to imagine situations in which BOLD signals would diverge quite strongly from the observed physiological responses. Collectively, these caveats demonstrate the potential problems of intercalated neuronal spiking properties for brain-imaging studies. Indeed, BOLD activation is typically not reported in posterior cingulate cortex in studies of risky decision-making in human subjects (Huettel et al., 2006; Kuhnen and Knutson, 2005; Tom et al., 2007). Lack of BOLD signal in posterior cingulate cortex
Neurons in many brain areas exhibit diverse, and sometimes contradictory, functional roles, demonstrating that functional properties are often heterogeneous. Such intercalations are unlikely to be detectable using conventional fMRI methods. Table 14.1 lists several examples of heterogeneous functional properties of single neurons within a single brain.

### Table 14.1 Examples of intercalated functional effects among neurons

<table>
<thead>
<tr>
<th>Area</th>
<th>Effect</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIP</td>
<td>Gaze following</td>
<td>Positive responses to gaze cue vs negative responses to gaze cue</td>
<td>Shepherd et al. (2009)</td>
</tr>
<tr>
<td>ACC</td>
<td>Conflict</td>
<td>Turns out to be direction selection</td>
<td>Nakamura et al. (2005)</td>
</tr>
<tr>
<td>CGp</td>
<td>Reward outcomes</td>
<td>Positive responses to outcomes vs negative responses to outcomes</td>
<td>Hayden et al. (2008a)</td>
</tr>
<tr>
<td>CGp</td>
<td>Reward tuning</td>
<td>Positive tuning for reward vs negative tuning for reward</td>
<td>McCoy et al. (2003)</td>
</tr>
<tr>
<td>Area 46</td>
<td>Direction tuning</td>
<td>Tuning for different directions in working memory</td>
<td>Funahashi et al. (1989)</td>
</tr>
<tr>
<td>striatum</td>
<td>Reward tuning</td>
<td>Positive and negative reward encoding (TANs medium spiny neurons)</td>
<td>Aosaki et al. (1995)</td>
</tr>
<tr>
<td>LIP</td>
<td>Numerosity tuning</td>
<td>Positive and negative tuning for numerosity</td>
<td>Roitman et al. (2007)</td>
</tr>
<tr>
<td>OFC</td>
<td>Decision variables</td>
<td>Various variables related to reward and decision-making</td>
<td>Kennerley et al. (2008)</td>
</tr>
<tr>
<td>LIP</td>
<td>Saccade tuning</td>
<td>Neurons and anti-neurons</td>
<td>Shadlen and Newsome (1996)</td>
</tr>
<tr>
<td>ACC</td>
<td>Reward tuning</td>
<td>Positive and negative responses</td>
<td>Matsumoto et al. (2007)</td>
</tr>
<tr>
<td>ACC</td>
<td>Reward variable tuning</td>
<td>Recent history vs RPEs</td>
<td>Seo and Lee (2007)</td>
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<tr>
<td>hippocampus</td>
<td>Learning-related changes</td>
<td>Positive vs negative learning related</td>
<td>Wirth et al. (2003)</td>
</tr>
<tr>
<td>ACC</td>
<td>Task stage</td>
<td>Explore vs exploit</td>
<td>Procyk et al. (2000)</td>
</tr>
<tr>
<td>ACC</td>
<td>Task stage</td>
<td>Each of four task events</td>
<td>Shidara and Richmond (2002)</td>
</tr>
<tr>
<td>OFC</td>
<td>Value encoding</td>
<td>Chosen value vs offer value vs taste</td>
<td>Padoa-Schioppa and Assad (2006)</td>
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<tr>
<td>striatum</td>
<td>Action value</td>
<td>Left vs right</td>
<td>Samejima et al. (2005)</td>
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<tr>
<td>amygdala</td>
<td>State encoding</td>
<td>Positive vs negative</td>
<td>Belova et al. (2008)</td>
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<tr>
<td>entorhinal</td>
<td>Match encoding</td>
<td>Match enhancement vs match suppression</td>
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</tr>
<tr>
<td>OFC</td>
<td>Operant phase</td>
<td>Specific phases</td>
<td>Kravitz and Peoples (2008)</td>
</tr>
<tr>
<td>ACC/DLPFC</td>
<td>Reward variable</td>
<td>S-R, reward-error, timing</td>
<td>Niki and Watanabe (1979)</td>
</tr>
<tr>
<td>LPFC</td>
<td>Reward context</td>
<td>Reward value independent of category and reward value within context</td>
<td>Pan et al. (2008)</td>
</tr>
<tr>
<td>hippocampus</td>
<td>Outcome encoding</td>
<td>Positive and negative responses to rewards</td>
<td>Wirth et al. (2009)</td>
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during risky decision-making may reflect the highly heterogeneous and intercalated functional response properties in CGp. The converse problem is just as vexing. If we had BOLD signal from CGp or any other brain region, it would be nearly impossible to infer the underlying neuronal spiking events in the absence of corresponding single-unit data. These results point to another problem raised by our findings. We showed that CGp neurons multiplex information about multiple variables related to risky decision-making, including reward variance, whether a risky option will be chosen, and the reward outcome of the previous two or three trials. This type of multiplexing is quite common in neuronal spiking patterns but is often overlooked in neuroimaging studies, which typically rely on analytical subtraction of two conditions to generate a signal. This technique leads to a preponderance of studies reporting that a brain region mediates a single cognitive process. In the extreme case, this can lead to neurorealism, the reification of a hypothesized theoretical variable based on a neural correlate (Racine et al., 2005).

14.1.2 Case study 2: neural representation of fictive outcomes

People routinely recognize and respond to information about outcomes that would have occurred had they chosen differently (Byrne, 2002; Camille et al., 2004; Chiu et al., 2008; Epstude and Roese, 2008; Lohrenz et al., 2007; Roese, 1997; Ursu and Carter, 2005). Such outcomes are known as fictive or counterfactual outcomes. The ability to understand such outcomes may be a precursor to the emotion of regret and is a hallmark of higher cognitive functions (Camille et al., 2004; Coricelli et al., 2005; Coricelli et al., 2007; Hofstadter, 1979; Ursu and Carter, 2005).

Two recent neuroimaging studies have examined the neural bases of fictive learning and reasoning (Chiu et al., 2008; Lohrenz et al., 2007). In one study, people played a stock market simulation game in which they found out what outcomes they could have obtained had they chosen differently (Lohrenz et al., 2007). The authors found BOLD activation in the ventral caudate nucleus of the striatum that reflected fictive outcomes. Moreover, they found that the size of these activations predicted the size of subsequent adjustments in behavior. A subsequent study reported that, although fictive information activates these same areas in the brains of smokers, the observed activations did not predict behavior (Chiu et al., 2008).

To complement these studies, we measured neuronal spiking in anterior cingulate cortex (ACC) while monkeys responded to fictive reward outcomes (Hayden et al., 2009a). To do this, we developed a novel task that provided information about rewards associated with options that could have been chosen (Fig. 14.3a). On each trial of our eight-point gambling task, monkeys chose one of eight identical-looking targets arrayed in a circle. Through training, the monkeys learned that seven of these targets provided a small and fixed reward (low-value, or LV target), while the other one provided a variable, but usually larger, reward (high-value, or HV target). The location of the HV target changed in a stochastically predictable manner from trial to trial by remaining in the same position with a 60% probability and moving one position clockwise with a 40% probability. Following choices, the outcome associated with each of the eight targets was revealed by
a change in their color. Thus, when monkeys chose one of the small, safe options—which they did on about 50% of trials—they learned the size of the reward they would have obtained had they chosen the HV target. We called this “could-have-been” reward the fictive outcome (Hayden et al., 2009a).

Monkeys successfully chose the HV target on about 45% of trials, which is about 75% of the accuracy of an ideal observer. Critically, the likelihood that a monkey would successfully choose the HV target on a trial depended strongly on the fictive outcome on the previous trial (Fig. 14.3B). Thus, monkeys recognize and respond to fictive outcomes in a way that is very similar to the way people do. We next recorded spiking activity of single neurons in the anterior cingulate cortex while monkeys performed this task. The ACC is a brain region that contributes to several cognitive processes, including representing uncertainty (Behrens et al., 2007; Rushworth and Behrens, 2008), representing effort costs (Rudebeck et al., 2006a), social decision-making (Hadland et al., 2003; Rudebeck, 2006b), and, most relevant for our study, representing reward outcomes and signaling subsequent adjustments in behavior (Amiez et al., 2006; Holroyd and Coles, 2002; Matsumoto et al., 2007).

We found that ACC neurons fire a clear phasic burst of action potentials following sac- cades to targets in this task, and that the size of this burst is a roughly linear function of the amount of reward expected on trials when the monkeys chose the HV target (Fig. 14.3C). Importantly, firing rate was also a roughly linear function of the amount of fictive reward signaled on trials when the monkeys choose the LV target (Fig. 14.3D). Spiking activity was generally higher for larger outcomes—a positive monotonic encoding—and this trend was observed for both experienced and fictive outcomes. A plurality of individual neurons exhibited significant correlations between firing rate and both types of outcomes. These results demonstrate that ACC neurons signal both experienced and fictive outcomes, and do so using a similar coding scheme, in their spiking activity.

One the one hand, these results appear to be more straightforwardly amenable to comparison with neuroimaging data than our results studying the neuronal spiking correlates of risk in CGp, since there was a low degree of heterogeneity of neuronal tuning for fictive rewards. However, given a BOLD signal, without knowledge of the underlying single-unit responses, one would not know whether separate populations of intercalated neurons encoded fictive and experienced rewards or whether a single population encoded both types of rewards. Thus, as in the other case study, the possibility that there might be neurons with distinct functional properties potentially clouds the interpretation of any neuroimaging study.

We also observed that individual neurons fired more weakly overall to fictive outcomes than to experienced outcomes. This asymmetry can potentially pose another challenge for understanding the relationship between BOLD and SUA. If we assume, for simplicity, that BOLD activation is a roughly linear function of neuronal spiking activity (see below), then activation will be stronger for experienced than for fictive outcomes. In voxels that are homologous to the ones we recorded, different BOLD changes would be observed, but in more distant voxels, BOLD activity may just barely cross the threshold for significance.
for experienced outcomes, but may fall just below it for fictive outcomes. Consequently, there will be voxels that appear to encode experienced outcomes but not fictive outcomes. Consequently, it may appear that these two outcomes have distinct spatial activation patterns, and thus are mediated by distinct neuronal processes.

In fact, the two neuroimaging studies that have studied fictive learning and reasoning found results that only partially overlapped ours. Specifically, Lohrenz and colleagues found no activation in ACC associated with fictive outcomes. The lack of effects observed

**Fig. 14.3** Fictive learning and spiking activity. (A) Schematic of task used to study fictive learning in monkeys. Monkeys are presented with an array of eight identical targets arrayed in a circle and a small, yellow, fixation square in the center. On acquisition of fixation, the square shrinks, and fixation is maintained for 500 ms. Following this, square disappears, and monkey saccades to one of the targets. Immediately following choice, information about the reward that would have been obtained for each of the eight targets is revealed by a change in color of each target. Following another half second, reward corresponding to chosen target is provided. Monkey is attempting to choose variable high-value target (here, green square) and not the seven low-value targets. (B) Likelihood of correctly choosing the high-value target on a trial following choice of LV targets depends on the fictive outcome on previous trial (black line). Following HV choices, likelihood is affected by whether HV target provided zero reward or other reward (gray line). (C) and (D) Firing rates of ACC neurons following choices depends on both experienced (C) and fictive (D) outcomes (panels A–D, Hayden et al., 2009a). Monkeys understood the values of the targets by their colors. Colors in these panels indicate reward category experienced by monkey: black (zero reward), red (low-value reward), green (medium rewards) and orange (high-value rewards).

in ACC, where we observed changes in neuronal spiking rate, may reflect any of the reasons expressed above, including fundamental differences between the information measured by single unit activity and BOLD, as well as task differences, species differences in neural processing as well as species differences in strategy. The study by Chiu and colleagues similarly found no main effect of fictive outcomes in ACC. However, BOLD activity in this region was positively correlated with the interaction between cigarette craving and fictive outcomes. Together, these results present a mixed picture of consistency between BOLD and single-unit data.

14.2 Model selection and the nature of animal and human behavior

Aside from differences in the way brain events are measured, single-unit physiology and functional neuroimaging generally employ different model organisms that differ in many fundamental ways. The differences in these organisms strongly constrain the behavioral tools that can be used in these methods, thereby strongly influencing the type of information gathered. Thus, these distinctions lead directly to important differences between fMRI and single-unit studies in cognitive neuroscience and neuroeconomics. Consider decision-making in the face of risk. Humans are generally regarded as risk-averse (Holt and Laury, 2002; Rabin and Thaler, 2001; Samuelson, 1977; Tom et al., 2007; Von Neumann and Morgenstern, 1944), while animals are often risk-seeking (Hayden and Platt, 2007; Hayden et al., 2008a, 2008b; McCoy and Platt, 2005).

In a typical experiment, humans are offered a single choice between a certain reward and a gamble associated with a larger and a smaller reward (or losses; see, e.g., Hayden and Platt, 2009b; Huettel et al., 2006; Kuhnen and Knutson, 2005). Animals cannot spontaneously understand explicit verbal or symbolic offers, and so must be trained to associate outcomes with prior events and choices over multiple, repeated trials. Learning from experience demands the use of specialized neural machinery for forming associations that differs from the mechanisms used to glean information from explicit instructions. Explicit cuing of task parameters has behavioral consequences as well; in the domain of risk, even in humans, trial repetition tends to promote risk-seeking (Hertwig et al., 2004; Lopes, 1981, 1996; Wedell and Boeckenholt, 1994; Barron and Erev, 2003), and is thus not favored in many economic studies. More importantly, this difference suggests that behavior for one-shot and repeated gambles—whether in humans or animals—may reflect distinct cognitive processes.

Our own work suggests that the way experiments are conducted with animal and human subjects has profound effects on behavior, and thus colors our interpretation of the underlying neurobiology. For these reasons, we advocate using behavioral methods that are closely analogous, if not identical, in comparative studies using fMRI in humans and single-unit physiology in animals. For example, if one is faced with multiple gambles with a positive expected value (amount multiplied by probability of reward), one has the opportunity to make up for stochastic losses. In other words, as the gamble repeats, the law of large numbers ensures that the possibility of bad luck is reduced and the average
payoff regresses toward expectation (Lopes, 1981). Indeed, many people switch their risk preferences when faced with multiple repeats of a single gamble (Hertwig et al., 2004; Lopes, 1981, 1996; Samuelson, 1963; Wedell and Boeckenholt, 1994).

For comparison, we studied this problem in rhesus monkeys—the favored animal model in single-unit studies in cognitive neuroscience and neuroeconomics (Hayden and Platt, 2007). Specifically, we examined the influence of delays between sequential choices on risk...
preferences in rhesus monkeys. We found that increasing the normally short inter-trial interval from 1 s to 45 s reduced risk-seeking (Fig. 14.4A). The precise pattern of decrease in risk-seeking was well-explained by a model that specifically assumes that the monkey makes prospective judgments over the next several trials, amortizing any potential loss from the present choice by the increasing probability of a potential gain in the long run (Rachlin et al., 1988). Increasing delays reduces this amortization, and thus induces more frequent choices of the guaranteed option (Hayden and Platt, 2007). These results are consistent with the idea that one-shot gambles and repeated gambles recruit different cognitive processes, including prospective thinking and interval timing (Hayden and Platt, 2007).

Risk is not the only domain in which task repetition may influence behavior and the cognitive processes that support it. For example, when human subjects are asked to decide on which candy bar they will receive for the next several weeks, they are more variety-seeking than they are when they decide each week which candy bar to take (Simonson, 1990). Trial repetition also impacts behavior in complex choice tasks, where behavior reflects low-level biases, such as alternation and perseveration (Lau and Glimcher, 2005), as well as local estimates of reward rate (Corrado et al., 2005; Hayden et al., 2008a; Lau and Glimcher, 2008). Trial repetition can influence choice and normative strategy in game theoretic contexts as well. For example, Nash equilibrium strategy can switch from defection to tit-for-tat when moving from a single-shot to an iterated Prisoner’s Dilemma problem (Axelrod, 1984). Behavior is influenced by the outcomes of recent trials in both simple discrimination tasks (Law and Gold, 2009) and in more complex executive control tasks (Emeric et al., 2007), and some functions may be improved by practice (Muraven et al., 1999). These and other effects of trial repetition indicate the importance of care in comparing experiments in which the amount of repetition can vary—especially when comparing fMRI results with humans to physiological studies with animals.

There is another potentially important difference between experiments structured around sequences of trials and those structured around one-time decisions. In one-time decisions, subjects do not have experience with previous trials, whereas in trial sequences, they may. In primate studies, where primary rewards are used exclusively, subjects inevitably have information about outcomes of previous trials. In many studies of risky choice in humans, even with sequences of gambles, the gambles are not resolved until the end of the session. It is generally assumed, in most animal experiments, that the task is well-learned and thus that behavior does not reflect the history of recent rewards and choices. This assumption does not generally hold, however (Corrado et al., 2005; Hayden et al., 2008a; Lau and Glimcher, 2008; Sugrue et al., 2004). For example, we found that choices made by monkeys in a simple gambling task strongly reflect reward outcomes of the most recent trials (Hayden et al., 2008a, 2009a). These patterns are consistent with simple reinforcement learning models, suggesting that learning continues, even after a task is well practiced. Such behavioral adjustment is strong enough that it occurs even for fictive outcomes—rewards that have been observed, but not directly experienced (Hayden et al., 2009a). In both cases, outcomes were found to contribute to neuronal spiking as well, thus underscoring the importance of repetition frequency and learning in neurophysiological studies with animals.
Yet another difference is that animals typically work for primary rewards that they consume immediately, such as food or drink (but see Seo and Lee, 2009). The use of primary rewards as motivators may strongly influence decisions (McClure et al., 2007). Moreover, since motivation must be maintained across multiple trials, animals are typically given very small rewards on each trial. It is generally assumed that satiety does not occur in most human studies—particularly those involving monetary rewards—and that diminishing marginal utility for goods does not apply to the small rewards typically used in the lab. In any case, small non-hypothetical rewards promote risk-seeking in humans, possibly because they engage different cognitive processes than those engaged by hypothetical or extremely large rewards (Barron and Erev, 2003).

To address these issues, we investigated the importance of task design in risky decision-making. We examined choices made by undergraduates in a gambling task that was as close as possible to the one we use with monkeys (Hayden and Platt, 2008). Specifically, thirsty participants sat in an anechoic chamber with a juice tube in their mouth, saw the same computer display that monkeys do, and received squirts of Gatorade of variable volumes as rewards. The rules were only explained in a minimal way, so that participants would have to learn the task structure and probabilistic nature of rewards by experience. We found that, under these conditions, risk aversion disappeared, and choices depended strongly on recent reward outcomes—just like the behavior of monkeys in the same situation (Fig. 14.4B, Hayden and Platt, 2008; Hayden et al., 2008a; McCoy and Platt, 2005).

In summary, the specific experimental paradigms used to study risk-sensitive decision-making in animals clearly deviate from the standard questionnaire approach used in behavioral economics. However, this does not mean that either one of these approaches is inferior or unrealistic. Indeed, real-life economic choices come in many forms, and any complete theory of the psychology and neuroscience of decision-making must account for all of them. More generally, laboratory measures of psychological processes should demonstrate their generality to real-life situations.

### 14.3 Establishing behavioral homologies

The above discussion highlights the critical importance of simple, straightforward behavioral studies designed to determine how behavior, and its underlying neural mechanisms, vary across different experimental task domains. Within the realm of risk, an important series of studies has looked at how decisions are influenced by learning through experience (Barron and Erev, 2003; Erev and Barron, 2005; Hertwig et al., 2004; Klos et al., 2005; Stewart et al., 2006). Furthermore, the application of reinforcement learning theory to the study of decision-making in uncertain environments has made it possible to take advantage of local reinforcement dynamics in studying risky decisions (Corrado et al., 2005; Dorris and Glimcher, 2004; Lau and Glimcher, 2005, 2007, 2008; Sugrue et al., 2004). Finally, it is critical to obtain input from experts in both qualitative and quantitative aspects of animal behavior, as they can provide a useful assessment of the applicability of economic models and tests to animal behavior (Bateson and Kacelnik, 1997; Kacelnik and Bateson, 1996; Stephens and Anderson, 2001; Stephens and Krebs, 1986; Stephens and McLinn, 2003).
One possible way to aid communication between physiologists and neuroimagers is to examine the behavior of humans making decisions about primary rewards—the currency of choice in animal studies. It is, in practice, very difficult to provide primary rewards to humans while they are in an MRI machine—although a few recent studies have either done so or come close (McClure et al., 2007; O’Doherty et al., 2002; Plassmann et al., 2007). One potentially valuable tool in this regard is the use of photographs, especially pictures of other people, which have been demonstrated to have reward value for individual subjects (Aharon et al., 2001; Hayden et al., 2007; O’Doherty et al., 2003). For example, we recently showed that the decisions men make about viewing photographs of females are consistent with economic theory in three ways (Fig. 14.4C, D; Hayden et al., 2007). First, opportunities to view photographs are discounted with time; second, they substitute for monetary rewards; third, they reinforce work (see also Aharon et al., 2001).

In fact, such photos activate the same reward circuitry as other types of rewards like food and money (Aharon et al., 2001; O’Doherty et al., 2003). Photographic rewards are experimentally appealing, as they do not diminish in value with satiety; do not require movements that introduce artifacts, such as swallowing; cannot be saved (thus promoting discounting); and are not messy and sticky, as many food rewards are.

A second solution is to train non-human animals to perform tasks that are more similar to those used in studies with humans. We have begun preliminary studies using explicit symbolic stimuli that do not require complicated reward-learning—similar to using symbolic task instructions with human subjects (Hayden et al., 2008c) see also (So and Stuphorn, 2008). These preliminary studies demonstrate that it is possible, in theory, for monkeys, at least, to use explicit cues about the probability, timing, and size of rewards.

Using novel tasks to enhance comparability between studies with humans and animals is advisable for a range of economic problems, such as delay discounting, economic exchange (Deaner et al., 2005; Klein et al., 2008), and strategic interactions.

Perhaps most importantly, all these behavioral approaches should inspire the use of neuroimetric measures to infer whether different decision problems are mediated by the same neural substrates (Britten et al., 1996; Glimcher, 2003; Kable and Glimcher, 2007; Klein et al., 2008). If, for example, risky decisions based on experiential learning engage brain regions distinct from those engaged by risky decisions based on verbal instructions, this will have important implications for related studies such as those designed to examine whether preferences for risk and time are mediated by the same underlying brain mechanisms.

14.4 Conclusion: a call for parallel studies using fMRI and single-unit recording in neuroeconomics and cognitive neuroscience

fMRI and single-unit activity, and other measures of brain function, are useful to cognitive neuroscience and neuroeconomics only to the extent that they can provide insight into the mechanisms underlying behavior. We have argued that the information offered by these measures is substantially different, and that understanding the nature of these differences is critical for developing a synthetic understanding of brain function.
These differences are manifest in two case studies from our own laboratory. We showed that monkeys’ risk preferences diverge strikingly from those of humans, and that these differences may reflect the specifics of task design, rather than fundamental species’ differences in behavior and cognition. Moreover, although spiking of neurons in CGp tracks several variables related to risky decision-making, distinct populations of neurons with different functional properties and that multiplex multiple forms of information frustrate any attempt to resolve CGp activity into a single aggregate response like BOLD. Consequently, the corresponding BOLD signal remains difficult to predict, and, conversely, it seems unlikely that these neuronal response patterns could be inferred based on fMRI data alone. We also showed that spiking of single ACC neurons tracks both experienced and fictive outcomes, and do so in a monotonic fashion. The critical finding of this study—that single neurons rather than overlapping populations—track both experienced and fictive outcomes in their spike rates, would be invisible to fMRI analysis, as would the precise time-course of these signals—at least given current imaging techniques. Moreover, the weaker, but still significant effects of fictive outcomes relative to experienced outcomes, could potentially lead to the conclusion that subregions within the ACC are specialized for experienced and fictive outcomes.

Based on these case studies, we argue that a deeper comprehension of brain function demands a fuller understanding of the discontinuities between behavioral methods used by physiologists and neuroimagers. Nonetheless, we contend that the single, largest problem is the fundamental uncertainty in the nature of the hemodynamic response. Beginning with Cajal, a large body of foundational literature has supported the centrality of synaptic transmission and single-neuron activity for computation in the brain (Barlow, 1972; Bullock, 1959). However, despite nearly 20 years of progress, the biophysical processes underlying the BOLD signal are less well-understood than those associated with neuronal spiking. Yet clear biases in neuronal selection and recording, the difficulty of recording from multiple areas simultaneously, and the limitations of an animal model, warrant caution in the abstemious focus on single-unit recording as the ultimate arbiter of neuroscientific understanding. Clearly, progress is being made; however, until a much more sophisticated understanding is obtained, we must resist the urge to rush to strong conclusions based on fMRI or single-unit data alone.

An often ignored, yet critical, set of differences between fMRI studies and single-unit studies comes in the form of experimental design. Indeed, two otherwise analogous experiments designed to isolate a cognitive variable of interest may have entirely different implementations in a single-unit study in an animal and an imaging experiment using human participants. Such differences can have direct ramifications on how these cognitive processes are recruited, and this difference can in turn influence neural data acquired. We therefore heartily endorse studies designed to directly examine the influence of the specifics of task design on both behavior and brain function.

Given these considerations, methodological convergence will demand an understanding of neural processing at multiple levels—ideally in animals and humans performing precisely the same tasks. The emergence of sophisticated data collection hardware,
increasing access to intracranial recordings in humans (albeit in rare and restricted circumstances), and rich new analytical methods, will facilitate this process. A fundamental goal of such studies should be to continue to delineate the relationships between SUA, LFPs, and BOLD in various cognitive states and processes. Coupling functions between these measures will most likely depend on location within the brain, as well as various cognitive and non-cognitive factors. It will be equally important to more fully understand the suite of biophysical processes that contribute to spiking, including dendritic computation, signal summation, neuromodulation, local inhibition, and so on. In these endeavors, the use of fMRI and single-unit physiology on the same monkeys, while they perform the same tasks, will be an invaluable tool—a method that is much easier and more practical than recordings in humans. This coordination of methods will permit perfect control for species, for specific subject, for idiosyncrasies in task design, and cognitive variability. Finally, it is paramount to perform single-unit physiology studies on humans when the rare opportunity arises, so as to reduce the potentially confounding effects of species’ differences in brain function and task demands. If all these measures can be successfully combined, their separate domains of information are likely to be quite beneficial for neuroscience, since averaging multiple independent sources of information generally reduces entropy (Shannon and Weaver, 1963).

References


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