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ON BUILDING A BRIDGE BETWEEN BRAIN AND BEHAVIOR

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■ **Abstract** Cognitive neuroscience is motivated by the precept that a discoverable correspondence exists between mental states and brain states. This precept seems to be supported by remarkable observations and conclusions derived from event-related potentials and functional imaging with humans and neurophysiology with behaving monkeys. This review evaluates specific conceptual and technical limits of claims of correspondence between neural events, overt behavior, and hypothesized covert processes examined using data on the neural control of saccadic eye movements.

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INTRODUCTION

Many authors write with conviction that the correspondence of the mental with the neural is so secure that an ultimate theory of mental phenomena will reduce to neural terms (e.g., Churchland 1986, Crick 1994). Others argue that mental states depend on but are not reducible to the physical states of the brain (e.g., Davidson 1970, Fodor 1981, Pylyshyn 1984). Determining whether the mental reduces to or emerges from the neural cannot be accomplished without correctly describing the mapping between the two.

Inferring Mechanism from Behavior

Before the development of methods to monitor brain states during behavior, physiological mechanisms could be inferred only from behavioral testing. Nevertheless, in the nineteenth century investigators began to articulate the correspondence between mental and physical processes. For example, Mach wrote, "To every psychical there corresponds a physical, and conversely. Like psychical processes correspond to like physical, unlike to unlike. . . . Particulars of the physical correspond to all the particulars of the psychic" (Boring 1942). Even philosophers who advocate a nonreductionist position acknowledge a mapping between mental and physical processes—"Although the position I describe denies there are psychophysical laws, it is consistent with the view that mental characteristics are in some sense dependent, or supervenient, on physical characteristics. Such supervenience might be taken to mean that there cannot be two events alike in all physical respects but differing in some mental respects, or that an object cannot alter in some mental respect without altering in some physical respect" (Davidson 1970). Such a position can be translated into an effective research strategy according to the proposition that ". . .whenever two stimuli cause physically indistinguishable signals to be sent from the sense organs to the brain, the sensations produced by these stimuli, as reported by the subject in words, symbols or actions, must also be indistinguishable" (Brindley 1970). Application of this principle in sensory detection or discrimination experiments permits testing hypotheses about physiological processes.

Another approach to understanding the mechanisms responsible for behavior has been through mathematically precise models of cognitive processes tested against detailed measurements of performance (e.g., Townsend & Ashby 1983; Luce 1986, 1995). Unfortunately, cognitive psychology abounds with alternative models with mutually exclusive architectures or algorithms, many of which are difficult or impossible to distinguish through behavioral testing. For example, choice behavior can be accounted for by sequential sampling models in which a single accumulator represents the relative evidence for two alternatives (e.g., Ratcliff & Rouder 1998). An alternative to a random walk of a single accumulator between alternatives is a race among multiple accumulators representing each alternative (e.g., Bundesen 1990, Logan 2002). In fact, models with single or multiple accumulators can account for common sets of data (Van Zandt & Ratcliff 1995,

Van Zandt et al. 2000), highlighting the limitations of arriving at secure inferences about mechanism based only on behavior (e.g., Uttal 1997). The theoretical issue has been articulated most definitely in the theory of finite automata (Moore 1956). It has been proven that given any computer with a finite number of inputs, outputs, and internal states and any experiment that determines the mapping of outputs to inputs, there exist other computers that are experimentally distinguishable from the original computer for which the original experiment would have given the same results. In other words, different architectures and algorithms can produce the same output from a given input.

Inferring Function from Neuronal Properties

The propositions quoted above were regarded initially as axiomatic, but the development of diverse means of monitoring neurophysiological processes directly or indirectly during behavior has afforded the unprecedented opportunity to investigate directly how mental processes relate to neural processes. Over the past decade numerous publications have carried titles like "Neural Correlate of X" where X is some cognitive capacity or behavior. For example, by monitoring the activity of neurons in macaque monkeys performing various tasks, this author has had opportunities to investigate neural correlates of visual perception (Logothetis & Schall 1989, Thompson & Schall 2000), attention and decision making (Thompson et al. 1996, Bichot & Schall 1999, Sato et al. 2001, Murthy et al. 2001; Sato & Schall 2003), response preparation (Hanes & Schall 1996, Hanes et al. 1998), and self-monitoring (Stuphorn et al. 2000, Schall et al. 2002). But what does "neural correlate" mean?

First, such attributions depend on whether the monkeys in these studies were perceiving, attending, deciding, preparing, and monitoring while the neural activity was recorded. A true mapping of neural and mental must be immediate; a mental state can only be supervenient on a neural state in the instant of occurrence. Now, neural states can be measured instantaneously through physiological methods. But, being subjective, mental states are not directly accessible for objective study, they can only be inferred from an overt response produced after the mental state has proceeded or even concluded. Measures of response time or accuracy can support the inference that some mental state occurred (Garner et al. 1956), but the mental state was *not monitored as it occurred*. Under such conditions a hypothesized link between neural state and mental state cannot be direct.

Second, to study neural correlates of some cognitive state, that state and the conditions for invoking and measuring it must be specified. Although obvious, many reports in the literature lay claim to a neural correlate of some cognitive state but present no converging behavioral measure of that state. Consider the confusion in the literature on neural correlates of cognitive factors influencing saccade production (Sparks 1999). Modulation of the activity of neurons in the superior colliculus has been ascribed to spatial attention (Goldberg & Wurtz 1972, Kustov & Robinson 1996), motor memory (Mays & Sparks 1980), response

selection (Glimcher & Sparks 1992), response preparation (Dorris & Munoz 1998, Dorris et al. 1997), motor set (Basso & Wurtz 1998), and target selection (Horwitz & Newsome 1999, McPeek & Keller 2002). This diversity of terminology probably exceeds the diversity of relevant cognitive processes. Therefore, an effective taxonomy of cognitive processes is needed that specifies the training and testing conditions necessary to invoke and manipulate the different cognitive processes. Fortunately, experimental psychologists have devised various means of probing stimulus encoding, attention, memory, response preparation, and error monitoring.

Third, neural activity associated with processes like stimulus encoding, attention, memory, and response preparation varies with history and context (e.g., Dorris & Munoz 1998, Bichot & Schall 2002). Thus, did a particular change in discharge rate occur because the stimulus was stronger or the subject was more attentive or was more prepared to respond or a different effector was to be used or because the payoff was better? A nomohistorical barrier prevents interpretation of raw brain states because each neuron is part of a brain that is part of an organism embedded in an environment at a particular point in history (Clark 1999).

It seems obvious that an understanding of mechanism requires a description of inner workings, and much research in basic neuroscience is motivated by the belief that function will be revealed through an accurate description of the properties of the brain. While form and function are deeply related in nervous systems (e.g., Leventhal & Schall 1983), descriptions of structural and physiological characteristics have not provided explanations of functions performed. This has been articulated most forcefully from the engineering perspective that distinguishes a functional level of explanation from distinct algorithms and physical instantiations (Marr 1982, Robinson 1992).

Thus, we face a conundrum. The same computation can be performed with different algorithms (e.g., single or multiple accumulators), so it is necessary to observe inner workings to understand the mechanism. However, the properties of the inner workings do not directly reveal function. How can we proceed? It seems that some kind of synthetic bootstrap is necessary.

LINKING PROPOSITIONS

The relationship between mental and physical descriptions can be articulated through linking propositions that specify the nature of the mapping between particular cognitive states and neural states (Brindley 1970, Teller 1984, Teller & Pugh 1983). Different kinds of linking propositions can be distinguished: identity, similarity, mutual exclusivity, simplicity, and analogy (the interested reader is directed to Teller 1984). A complete linking proposition encompasses a set of logical relations. The initial proposition states that identical neural states map onto identical cognitive states. The contrapositive of the initial proposition states that nonidentical cognitive states correspond to nonidentical neural states. These two statements are equivalent logically. The converse proposition states: identical

cognitive states map onto identical neural states, and the contrapositive of the converse states: nonidentical neural states entail nonidentical cognitive states. These two statements are logically equivalent. However, given the complexity in mapping mental and neural properties, the truth of the converse statement is not implied by or contingent on the truth of the initial proposition.

Testing Linking Propositions

The empirical evaluation of linking propositions raises several fundamental issues. First, what is meant by "identical"? Obviously, it must mean "statistically indistinguishable." Also, identity cannot refer to constancy within an individual over time; you cannot step twice in the same river. However, experimental psychology presumes rough identity across subjects because (absent clinical or other exceptions) common brain areas serve common functions across individuals. What about identity across species? Do brain structures that are homologous across species have common functional states producing common behaviors and cognitive states? It seems we must grant this at least for nonhuman primates. If not, then how can neurophysiological data from macaque monkeys be related meaningfully to human cognition? Extending such homologous identity to rodents or invertebrates seems less secure.

Second, at what behavioral and neural scale must the comparison be judged? Surely common mental states cannot require common states of each receptor and ion channel in the nervous system. If this were so, then we could not think the same thought twice. But, if the exemplar-based view of cognition is correct, then perhaps we never do (e.g., Barsalou et al. 1998). Also, if a molecular scale description is necessary, then we are faced with an effectively insurmountable challenge. Another of Moore's (1956) theorems proves that the number of steps needed to learn about the internal structure of a computing machine is at least the same order of magnitude as the number of states of the machine. Indeed, the ability to write the systems of equations describing the dynamics of a simple single cell does not confer the ability to solve those equations in a realistic period (Tomita 2001). The computational challenge of simulating neural networks large enough to be relevant for explaining behavior at a membrane scale in real time seems effectively insurmountable with current computational devices.

Fortunately, a molecular-scale description of a brain state may not be necessary. Cogent arguments have been made that the discharges of neurons constitute the most appropriate level of analysis of the computational function of the brain (Barlow 1995). However, it is well known that the discharges of neurons are typically quite variable for reasons that remain unclear (e.g., Softky & Koch 1993, Shadlen & Newsome 1998). Perhaps the copious variation in neural states may be irrelevant for evaluating meaningful linking propositions. Perhaps the states of brain corresponding to perceptions, thoughts, intentions, and emotions are fewer. Ultimately, it seems most likely that a useful identity between cognitive and neural processes resides at the level of some ensemble of neurons (and glia?) comprising

an anatomically interconnected network. Analyses of the reliability of the relationship between discharge rate and overt behavior indicate that the ensemble sufficient to account for performance can be as small as 10–100 neurons (Shadlen et al. 1996, Bichot et al. 2001). However, to produce an overt response, orders of magnitude more neurons are necessary (e.g., Newsome & Paré 1988, Schiller & Chou 2000, Schiller & Lee 1994). It seems that neurons selected at random from a pool can be an effective proxy for that pool because a degree of correlation exists in the activity of neurons within the pool. This suggests that in explaining behavior, the particular state of a particular neuron may not be necessary to specify. In other words, the variability observed in the activity of single neurons may overestimate the variability of the state embodied by the pool of neurons.

Finally, we must understand that the mapping of a linking proposition holds only for certain neurons, referred to as the bridge locus (Teller 1984, Teller & Pugh 1983). This is the population of neurons that comprise the most immediate substrate for the behavior and cognitive process. How can such neurons be identified? Positive evidence of a correspondence between the activity of neurons and the presence of a particular cognitive process is a good start, but the logic of exclusion is ultimately necessary (Platt 1964). All neurons that do not bear a predictable relationship with the behavior or cognitive state cannot be part of the bridge locus. In other words, the bridge locus is the set of neurons for which the linking proposition is not rejected.

Anatomical characteristics provide necessary, converging evidence. The first fact of neuroanatomy is that the brain is comprised of different types of neurons with a variety of morphological and ultrastructural characteristics, entertaining different connections. Localization of function has been at the heart of psychology and neuroscience since Bell and Magendie distinguished the sensory and motor roots of the spinal cord and Müller popularized the labeled lines of sensory processing (Boring 1942). Distinctions between functional types of neurons become much more complex further removed from the sensory or motor periphery; however, even in sensorimotor structures, proper testing can reveal neurons with different relations to covert processes and overt responses (e.g., Hanes et al. 1998, Horwitz & Newsome 1999, McPeek & Keller 2002, Sato & Schall 2003).

Connectivity is crucial converging evidence for admitting or excluding certain neurons from a bridge locus. Do the axons of the neurons in question convey spikes to the appropriate parts of the brain to instantiate the hypothesized process? For example, if a neuron does not innervate downstream motor structures, it seems extravagant to claim that activity of this neuron instantiates response preparation. Likewise, if a neuron innervates visual areas of the cortex, then it is incoherent to claim that the activity does not influence visual processing in some way. Thus, a bridge locus is a population of neurons interconnected in particular ways possibly across anatomically distinct parts of the brain with inputs suitable to convey the necessary signals and outputs appropriate to exert the necessary influence.

LINKING PROPOSITIONS ABOUT SACCADE PRODUCTION

A wealth of information and insight informs the evaluation of specific linking propositions concerning sensation and perception (e.g., Parker & Newsome 1998, Romo & Salinas 2003), but additional insights may be gained by exploring the linking propositions for the preparation and production of movements. We will focus on saccadic eye movements, the rapid shifts of gaze used to explore scenes, because so much is known about the mechanics of the movement and the neural signals responsible (e.g., Wurtz & Goldberg 1989, Carpenter 1991).

Saccades are produced by a pulse of force that rapidly rotates the eyes followed by a step of force appropriate to resist the elastic forces of the orbit and maintain eccentric gaze. This pattern of force is exerted on the eyes by muscles innervated by neurons in the brainstem (Scudder et al. 2002, Sparks 2002) (Figure 1). Burst neurons innervate the extraocular motoneurons to provide the high-frequency burst of spikes necessary to produce saccadic eye movements. Different burst neurons innervating different motor neurons that innervate different muscles discharge for saccades in different directions. The burst neurons are subject to potent monosynaptic inhibition from omnipause neurons. Omnipause neurons discharge tonically during fixation. Immediately prior to initiation of a saccade in any direction, omnipause neurons cease discharging, releasing the inhibition on the appropriate pools of burst neurons to produce the burst in the motor neurons necessary to shift gaze in the desired direction. Upon completion of the saccade, omnipause neurons reactivate to reinstate inhibition on the burst neurons. Tonic neurons with activity proportional to the angle of the eyes in the orbit are also present in the brainstem. These tonic neurons innervate motor neurons and are innervated by burst neurons. The activation from tonic neurons results in a measure of innervation of the motor neurons necessary to maintain eccentric fixation against the centripetal elastic forces of the orbit.

The neural events preceding activation of the brainstem saccade generator occur in a circuit distributed through particular areas of the frontal lobe (Schall 1997), the basal ganglia (Hikosaka et al. 2000), cerebellum (Thier et al. 2002, Lefevre et al. 1998), and superior colliculus (Munoz & Schall 2003, Munoz et al. 2000). This circuit conveys to the brainstem saccade generator where and when to shift gaze. The superior colliculus is organized in a topographic map of saccade direction and amplitude. The frontal eye field has a rougher map of saccade amplitude, and the frontal eye field and superior colliculus are connected topographically. Thus, the direction and amplitude of the saccade produced is dictated by the location in the map of the active population of neurons. However, neurons in the frontal eye field and superior colliculus have broad movement fields, so many neurons contribute to any saccade. The activity of the pool of neurons is combined as a vector average to produce the particular saccade. The neurons in the superior colliculus that generate saccades are under tonic inhibition from neurons in the rostral end of the superior colliculus and in the basal ganglia that are active during fixation.

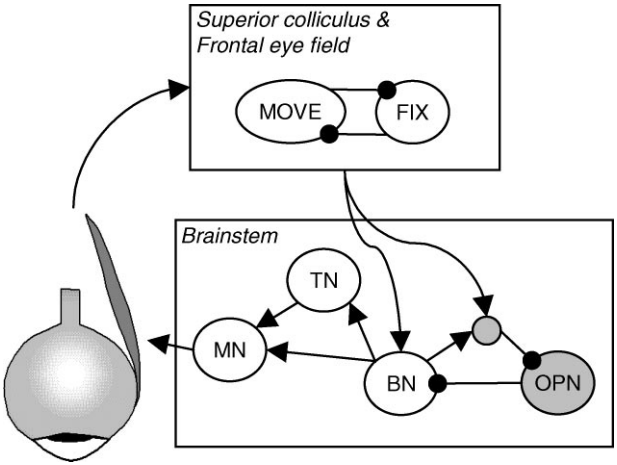

Figure 1 Simplified circuitry responsible for preparing and executing saccades. The extraocular muscles are innervated by motor neurons (MN) that produce a high-frequency burst of action potentials during saccades driven by burst neurons (BN). Tonic neurons (TN) integrate the burst to produce motor neuron activity necessary to maintain eccentric gaze. Burst neurons are under inhibitory control of omnipause neurons (OPN). The saccade generator in the brainstem receives signals for where and when to shift gaze from a circuit including the superior colliculus and frontal eye field, which consists of gaze-shifting movement neurons (MOVE) and gaze-holding fixation neurons (FIX). Movement and fixation neurons are also in reciprocal inhibitory relationship. Arrow ends signify excitatory connections and circle ends signify inhibitory connections.

Thus, another level of reciprocal inhibition outside the brainstem controls saccade production.

Influential models of this circuit formulate admirably specific propositions linking the mechanics and dynamics of saccadic eye movements, the properties of these neurons, and the control signals presumed necessary to produce saccades (e.g., Robinson 1975, Tweed & Vilis 1985, Scudder 1988, Lefevre et al. 1998; but see Robinson 1992). The discharge rate of burst neurons corresponds to eye velocity (at least for saccades less than 20 degrees). Tonic neurons are referred to as the neural integrator according to the hypothesis that they integrate the velocity signal of the burst neurons to signal eye position. Saccade termination is hypothesized to be controlled through a local feedback circuit that is driven by the error between the current eye position (or displacement) and the desired eye position (or displacement). According to these models, the discharge rate of the burst neurons corresponds to this dynamic motor error signal that creates the velocity signal to move the eyes.

Compelling evidence supports the hypothesis of a feedback control circuit. First, transient activation of the omnipause neurons while a saccade is in flight results in reduced eye velocity, even to nearly zero; however, when the omnipause

neurons are returned to their normal state, the saccade continues to completion, as if the error signal had not yet been expended (e.g., Kaneko 1996). Second, reversible inactivation of the burst neurons in the brainstem results in markedly slower saccades but the duration is increased proportionally to expend the error (Barton et al. 2003). The scope and power of these models should be admired. However, it is sobering to realize that fundamental questions remain unanswered (Sparks 2002). Some limitations are technical. For example, a comprehensive account of the relation of motor neuron activity to movements of the eye requires knowledge of the characteristics of the particular muscle fibers innervated by a given motor neuron, but at present it is not possible to monitor and selectively influence selected populations of cells simultaneously. Conceptual limitations also impede understanding. For example, the unfulfilled search for the mechanism that compares current with desired eye position (or displacement) suggests that perhaps current models make incorrect assumptions or lack essential overlooked features (e.g., Steinman 1986, Brooks 2001).

Evidence for Covert Response Preparation

Stimuli can be presented and overt responses measured. However, to explain orderly relationships between responses and stimuli, it is now regarded as useful if not necessary to hypothesize certain covert processes mediating the encoding, selection, and categorization of stimuli and preparation of responses. For example, the time of an overt response to a given stimulus is variable and unpredictable (Luce 1986). Within that unpredictability, though, certain trends have been observed. For example, when given a warning ("ready") before an imperative trigger signal ("go"), subjects respond earlier and more reliably than when no warning is given (Niemi & Näätänen 1981). But, this occurs only if the passage of time allows a sense of expectation (Näätänen 1971). Reaction time can also be influenced by repetition of stimuli or responses (e.g., Dorris et al. 1999, Carpenter 2001, Bichot & Schall 2002) or by success in previous trials (Rabbitt 2002). To explain this variation, one can hypothesize a process that transpires after a warning signal and is influenced by events in preceding trials to influence the readiness to initiate a movement. Such a covert process may be called response preparation. Further evidence for response preparation is the fact that partially prepared responses can be withheld if an imperative "stop" signal occurs (e.g., Osman et al. 1986, 1990). This ability can be explained by hypothesizing another covert process that prevents movements (Logan & Cowan 1984). Before continuing, it is important to be clear what is and is not meant by response preparation.

Response Preparation and Intention

Science travels on its terminology. Formulating effective linking propositions requires characterization of covert processes that is accurate, operational, and not extravagant. However, as indicated above, such is not always the case. For example, some authors have identified *intention* with neural modulation in the parietal

lobe of macaque monkeys preceding a movement (Snyder et al. 2000). Can neurophysiology reach this far?

The term intention is complex (e.g., Aune 1967). The disposition to perform some act is a central feature of an intention, but intention cannot be identified entirely with response preparation. A statement of intention must also answer, "Why was that done?" Of course, one answer can be the causal path through neurons to muscles, but this is incomplete. A satisfactory explanation must address the reasons for the action based on preferences, goals, and beliefs. In other words, to judge whether a movement was intended, one must refer to the agent's beliefs about which action must be performed under what circumstances to bring about the desired object of the intention. A consequence of this is that intentions may not be realized, but success can be judged only with reference to the description of the goal and the conditions under which it could be achieved (e.g., Heckhausen & Beckmann 1990). Furthermore, a particular movement may be intentional under one description but not under another. For example, an eye may wink or blink.

These concepts about intention have been formulated in the domain of human interactions. We cannot take for granted that they apply to animals used in neuroscience experiments. If animals cannot be said to have intentions, then information gained by invasive neurophysiology experiments cannot be related to intention. Fortunately, behavioral research describing communication and deception, for example, indicates that the attribution of intention to monkeys seems justified (e.g., Tomasello & Call 1997, Hauser et al. 2002). Certainly, abundant evidence confirms that response preparation can be studied in macaque monkeys.

Bridge Locus for Response Preparation

To discover the mechanism of response preparation, neural activity must be monitored when response preparation occurs. Therefore, subjects must perform a task that creates a state of readiness and an overt measure of that readiness. A prepared movement should be distinguished by some improvement in performance. Specific criteria for identifying a bridge locus for response preparation have been articulated (Riehle & Requin 1993). First, the neuronal discharge rate must change during a warning period before the movement. Second, the magnitude of neural modulation must be proportional to the likelihood of a movement being directed into the response field of a neuron. Third, the magnitude of neural modulation must be predictive of the probability of responding and of reaction time.

These criteria can be tested in tasks with instructional warning signals preceding imperative trigger signals. Early work described "preparatory set cells" in premotor cortex based on the observation that the neurons discharged following instructions and changed discharge rate if instructions changed (e.g., Wise & Mauritz 1985). But this attribution can be questioned because no relation was reported between neural activity and a measure of performance such as reaction time. In fact, reaction time was not affected by the waiting period; therefore, the state of preparation is not clear. Subsequent reports provided more directly concomitant neural and performance

data (Riehle & Requin 1993, Riehle et al. 1994). A cue provided complete, partial, or no information about the direction and extent of a wrist movement that was executed following an imperative trigger signal. Neural activity in primary motor and in premotor cortex was correlated with the changes in reaction time depending on the amount of information conveyed by the cue. The greater the activity, the shorter the reaction time, especially when the direction of the movement was cued. These data meet the aforementioned criteria. Similar data have been obtained in the superior colliculus of monkeys performing a saccade task with varying probabilities of target appearance at one of two locations (Dorris & Munoz 1998).

In general, neurons in the frontal eye field, basal ganglia, and the superior colliculus exhibit modulated discharge rates during a warning period that correlate with the variation of reaction time (reviewed by Munoz & Schall 2003). Often preparation results in undesirable, premature movements; sprinters know this. Preparation serves nothing if movements are initiated at the least measure of activation. Toward this end, the motor system seems designed to prevent preparation from producing too many premature movements. For example, omnipause neurons are not modulated at all during periods of saccade preparation (Everling et al. 1998). The maintenance of the inhibition of the omnipause neurons on the burst neurons prevents premature saccades.

Control of Saccade Initiation

A task known as countermanding provides another avenue for identifying neurons constituting the bridge locus of response preparation. This task was developed to investigate the control of thought and action (reviewed by Logan 1994). A subject's ability to control the production of movements is probed in a reaction time task by infrequently presenting an imperative stop signal. The subject is rewarded for withholding the movement if the stop signal occurs. Performance in the countermanding task is probabilistic. In a given trial, one can predict only to an extent whether a subject will cancel the partially prepared movement. The probability of inhibiting a movement decreases as the delay between the go signal and the stop signal increases. This unpredictability arises because reaction time is fundamentally stochastic. Obviously, movements generated with shorter reaction times can occur in spite of the stop signal if they are initiated before the stop signal influences the system. Likewise, movements that would occur after longer reaction times can be canceled if a stop signal occurs because enough time is available for the process elicited by a stop signal to interrupt response preparation.

Three measures of performance can be obtained—reaction time on trials with no stop signal, reaction time of trials that escape inhibition, and the probability of inhibiting the movement. These overt measures can be accounted for remarkably well by a very simple model consisting of two processes, a GO process and a STOP process, in a race with independent, random finish times (Logan & Cowan 1984; see also Lisberger et al. 1975, Becker & Jürgens 1979). The GO process initiates

the movement after presentation of the target. When no stop signal is given, only the GO process is active, so the distribution of reaction times in these trials is the distribution of finish times of the GO process. If the stop signal is presented after the target, then while the GO process proceeds, the STOP process may be invoked. If the STOP process finishes before the GO process, then the partially prepared movement is canceled. Alternatively, if the GO process finishes before the STOP process, then the movement occurs. Analysis of the overt behavior in terms of this race model affords an estimate of the duration of the covert STOP process, referred to as the stop-signal reaction time (SSRT); this is the interval required to cancel the movement that was being prepared.

A saccade version of this paradigm was developed for testing with macaque monkeys (Hanes & Schall 1995). Reinforcement was given following a saccade to a peripheral target that appeared when the fixation spot disappeared unless a stop signal was presented. The stop signal was reappearance of the fixation spot. If the stop signal appeared, reinforcement was contingent on withholding the saccade. The average SSRT for monkeys performing the saccade countermanding task is around 100 ms (Hanes & Schall 1995, Hanes et al. 1998). Performance of human subjects in the saccade countermanding task matches that of monkeys, although with slightly longer SSRT (Hanes & Carpenter 1999, Cabel et al. 2000, Logan & Irwin 2000, Asrress & Carpenter 2001, Colonius et al. 2001).

Relation of Neural Activity to Response Time

To understand how partially prepared saccades are canceled, first we must know how they are initiated. Current data show that saccades are initiated when the discharge rate of certain neurons in the superior colliculus and frontal eye field reaches a particular level, and this level does not vary with reaction time (Sparks 1978, Hanes & Schall 1996, Dorris et al. 1997) (Figure 2). The same relationship holds for activation in primary motor cortex before forelimb movements measured at the level of single neurons (Lecas et al. 1986) or at the level of an event-related scalp potential called the lateralized readiness potential (Gratton et al. 1988).

This relationship between discharge rate and reaction time holds for only a subset of the neurons encountered in these structures. The activity of neurons that have exclusively visual responses exhibits no relation to the time of saccade initiation (Brown et al. 2001). The neurons with activity that relates to saccade initiation time are specifically those that are modulated exclusively or particularly before saccades, even when no visual stimulus is present. Other research indicates that the axons of such saccade-related movement neurons project from the superior colliculus to the brainstem saccade generator (e.g., Raybourn & Keller 1977) and from frontal eye field to the superior colliculus and brainstem saccade generator (Segraves 1992, Segraves & Goldberg 1987, Sommer & Wurtz 2000). Consequently, electrical stimulation at the sites where saccade-related movement neurons are recorded elicits saccades with very low current levels while more current is needed to elicit saccades from sites where visually responsive neurons are encountered (e.g., Robinson 1972, Bruce et al. 1985).

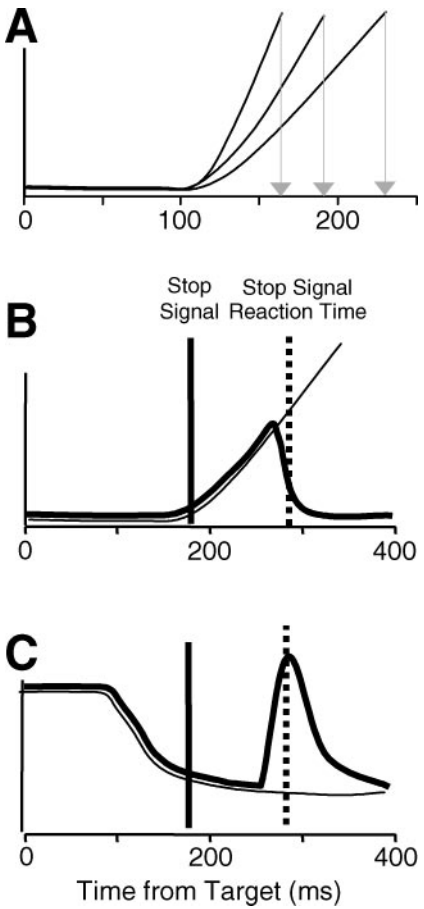

Figure 2 Stylized pattern of neural activity controlling the initiation of saccades. (*A*) Saccades are initiated when the discharge rate of movement neurons reaches a threshold level. The variability in reaction time originates in variability of the time taken for the neural activity to reach the threshold. (*B*) Comparison of activity of movement neurons in the superior colliculus and frontal eye field occurring during countermanding trials with no stop signal (thin) or trials with a stop signal in which the saccade was canceled (thick). Thick vertical line marks stop signal presentation. Dashed vertical line marks stop signal reaction time. When saccades are canceled, movement neuron activity that was increasing toward the threshold decreases rapidly, within the stop signal reaction time. (*C*) Comparison of fixation neuron activity during countermanding trials with no stop signal (thin) or trials with a stop signal in which the saccade was canceled (thick). When saccades are canceled, fixation neuron activity that was suppressed increases rapidly, within the stop signal reaction time.

Many models have been developed to explain the variability of reaction time under various conditions. Common sequential sampling models suppose that in response to a stimulus, some signal accumulates until it reaches a threshold, thereby triggering a response to the stimulus. One version supposes that the variability in reaction time arises from randomness in the level of the trigger threshold (e.g., Grice et al. 1982). Another version assumes that the threshold is constant and the variability in reaction time arises from randomness in the rate of growth of the accumulator (e.g., Carpenter & Williams 1995, Ratcliff & Rouder 1998). In fact, this is another instance in which different architectures cannot be distinguished by overt behavior (Dzhafarov 1993). The neurophysiological data indicate that the variability in saccade reaction time arises from variation in the rate of growth of the movement-related activity toward the trigger threshold (Figure 2). This observation of inner workings has been interpreted as evidence for the fixed-threshold, variable-growth architecture and against the variable-threshold, fixed-growth architecture (Hanes & Schall 1996).

Of course, this observation is relevant for distinguishing the alternative model architectures only if the population of neurons for which the observation holds is the bridge locus of the accumulator. This cannot be taken for granted. The accumulator conceived of in sequential sampling models is commonly regarded as the growth of evidence about alternative stimuli. Such models incorporate an additional sensory and motor transduction and transmission delay, but this is regarded as a fixed interval (e.g., Ratcliff & Rouder 1998, Usher & McClelland 2001). Recent neurophysiological studies have interpreted a slowly increasing neural activation as just such an accumulation of evidence (Gold & Shadlen 2000, Roitman & Shadlen 2002, Cook & Manusell 2002, Krauzlis & Dill 2002). This interpretation is strengthened by the possible correspondence between this neural signal and the ratio of the likelihood of the alternatives, which is an optimal decision variable (Gold & Shadlen 2001). However, none of these models or neural studies explains how satisfaction of a criterion of evidence can initiate a movement of the body.

As reviewed above, the original physiological evidence that movements were initiated when neural activity reached a threshold was obtained from neural signals that should be identified with response preparation (Gratton et al. 1988, Hanes & Schall 1996). Therefore, if the original models were about the form of the accumulation of evidence, then the pattern of movement-related activity seems irrelevant, unless one wishes to identify accumulating evidence with response preparation. However, such an identification is clearly incorrect. The distinction between accumulating evidence and preparing a response can be made explicit when an arbitrary mapping of response onto stimulus is introduced. For example, recent studies have demonstrated that arbitrary stimulus-response mapping (e.g., prosaccade versus antisaccade responses) changes the influence of electrical stimulation of frontal eye field (Gold & Shadlen 2003) and introduces measurable delays in the time taken to encode stimulus properties, select targets for saccades, and initiate movements (Sato & Schall 2003). The joint observations of variability in the time taken to accumulate evidence and variability in the time taken to prepare a response

coupled with the fact that arbitrary movements can be produced in response to a given stimulus seem to require a theoretical framework comprised of distinct, successive stages of processing (Sternberg 2001, Schall 2003).

The hypothesis that stimulus-guided behavior is the outcome of distinct, successive stages of processing entails unavoidable methodological and conceptual problems. For example, how can the finish times of successive stochastic stages be distinguished within the distribution of random reaction times? Also, are the transformations within and transmissions between stages continuous or discrete (e.g., Coles et al. 1985, Miller 1988)? Neurophysiological data from behaving monkeys can address these questions by measuring the duration of intermediate stages of processing through the evolution of neural activity in the frontal eye field of monkeys performing visual search (Thompson et al. 1996, Sato & Schall 2003, Sato et al. 2001). Also, it has been possible to show that the processes of saccade preparation assessed through the activation of saccade-related movement neurons is influenced by the properties of visual stimuli, which is evidence in support of the continuous flow between stages (Bichot et al. 2001). However, both of these observations are interpretable only insofar as the neural events that are measured map onto the relevant cognitive processes. Indeed, the fact that such conclusions hinge on this mapping highlights the necessary role of explicit linking propositions in reasoning about the relation between neural processes and the supervening functional processes.

Relation of Neural Activity to Movement Cancellation

The countermanding paradigm provides two criteria for determining whether a neuron comprises the bridge locus for saccade production. First, obviously, activation must be different when movements are produced versus not produced. Second, critically, the difference in activation when movements are canceled must occur within the SSRT, that is, within the time that the movement was canceled. Certain but not all neurons in the frontal eye field and superior colliculus meet these criteria (Hanes et al. 1998, Paré & Hanes 2003) (Figure 2). Neurons with saccade-related activity, which began to increase toward the trigger threshold, failed to reach the threshold activation level when saccades were canceled. Instead, when partially prepared saccades were canceled, the saccade-related activity decreased rapidly after the stop signal was presented. Moreover, the saccade-related activity associated with canceling as compared to executing the saccade became different just before the SSRT elapsed. A complementary pattern of neural activity was observed in fixation neurons. If eye movements were canceled, fixation neurons that had decreased firing generated a rapid increase of discharge rate before the SSRT. Notably, neurons with exclusively visual responses modulate not at all or too late when saccades are canceled. According to the logic of the countermanding paradigm, the activity of movement and fixation but not visual neurons in frontal eye field and superior colliculus is logically sufficient to specify whether or not a saccade will be produced and therefore comprise the bridge locus of saccade

preparation. The same conclusions can be drawn from the variation of the magnitude of the lateralized readiness potential in humans performing manual movements in a stop-signal task (De Jong et al. 1990, 1995; van Boxtel et al. 2001).

Alternative Propositions Mapping GO and STOP onto Neural Processes

The GO and STOP processes are defined at a functional level by the race model. How do they map onto brain processes? This seems deceptively simple to articulate, but we will proceed deliberately by considering three propositions: (*a*) GO and STOP map onto different cortical areas or subcortical structures, (*b*) GO and STOP map onto distinct kinds of neurons, and (*c*) GO and STOP map onto particular periods of activation of particular pools of neurons.

Consider the proposition that GO and STOP map onto distinct structures. Some reports have identified certain parts of the frontal lobe with response inhibition (e.g., Aron et al. 2003). However, as reviewed above, certain neurons are active in a manner sufficient to instantiate the GO and STOP processes, but others within the same structure decidedly do not. The heterogeneity of neurons in frontal eye field and superior colliculus compels rejection of the proposition that GO and STOP map onto distinct cortical areas or subcortical structures. Generalizing this conclusion to other parts of the brain and other tasks highlights the severe limits of inferences about mechanism possible from noninvasive measurements such as event-related potentials or functional brain imaging (Uttal 2001, Friston 2002).

Next, consider the proposition that GO and STOP map onto distinct kinds of neurons. In the context of saccade production, it seems sensible to identify the GO process with gaze-shifting (movement) neurons and the STOP process with gaze-holding (fixation) neurons. This simple interpretation is challenged, though, by the observation that when the GO process leads to a saccade, movement neurons exhibit increased discharge rate but *at the same time* fixation neurons exhibit decreased discharge rate (e.g., Dorris & Munoz 1998, Dorris et al. 1997) (Figure 2). Likewise, when saccades are canceled, fixation neurons exhibit a rapid increase in discharge rate while at effectively the same time movement neurons exhibit a rapid decrease in discharge rate (Hanes et al. 1998, Paré & Hanes 2003). As reviewed above, this coordinated pattern of activation probably comes about through reciprocal inhibition between fixation cells and movement neurons within and across structures. The concurrent modulation of the movement and fixation neurons associated with gaze shifting and gaze holding suggests rejection of the proposition that GO and STOP map exclusively onto distinct kinds of neurons.

Consequently, by exclusion the GO and STOP processes map onto periods of activation of particular sets of interconnected neurons in a distributed network. GO can map onto the coordinated increase of movement cell activity and decrease of fixation cell activity. STOP can map onto the neural events that occur in canceled trials—the concomitant rapid increase of fixation cell activity and decrease of movement cell activity. Current evidence indicates that this reciprocal activation

of movement and fixation neurons occurs through mutual inhibition (e.g., Munoz & Wurtz 1993b, Munoz & Istvan 1998, Quaia et al. 1999).

The proposition that the GO and STOP processes map onto common pools of interacting neurons poses a potential paradox—how can two processes racing with independent finish times emerge from a network of interacting units? Perhaps the formulation of a race between GO and STOP is flawed. Some reports have presented evidence inconsistent with the predictions of the race model (Colonius et al. 2001). However, this evidence amounts to the performance of rare, exceptional subjects. Moreover, an alternative account has not been formulated.

On the other hand, several lines of evidence are consistent with predictions of the race model. First, if the presence of the stop signal slowed the process of generating the movement, then the trials that are produced in spite of the stop signal should have slower reaction time. However, the reaction times of movements that escape inhibition correspond to the reaction times in trials with no stop signal with values less than the SSRT (Logan & Cowan 1984; Osman et al. 1986, 1990; Band et al. 2003). Second, if the presence of the stop signal interfered with the process of generating the movement, then saccade amplitude or velocity should be reduced. However, saccade amplitude and velocity are not different during noncanceled trials and trials with no stop signal (Hanes & Schall 1995). Third, if the response to the stop signal affected response preparation, then the neural processes leading to noncanceled movements should be different from those leading to movements when no stop signal occurs. However, neither the lateralized readiness potential (De Jong et al. 1990, van Boxtel et al. 2001) nor the activity of movement and fixation neurons in frontal eye field and superior colliculus (Hanes et al. 1998, Paré & Hanes 2003) are different between noncanceled trials and trials with no stop signal. Finally, weak violation of the finish time independence premise is not fatal; it only means that the estimate of the SSRT will vary as a function of stop-signal delay (De Jong et al. 1990, Band et al. 2003). Therefore, according to its effectiveness and elegance, we have no basis to reject the validity of the race formulation, so we must contend with the challenge of reconciling performance described by a race model produced by a mechanism comprised of interacting units.

The reconciliation hinges on a deeper understanding of the constitution of the GO and STOP processes. The Logan & Cowan (1984) race model assumes stochastic independence of the finish times of GO and STOP processes. The model says nothing about the means by which the process reaches the finish times. The model is also mute about what happens after either process finishes, beyond requiring that the completion of the STOP process interrupts the GO process and vice versa. The model is not explicit about how this interaction occurs or about how the GO and STOP processes are reset. The key to understanding how independent finish times can arise from interacting elements is to realize that SSRT measures the *end of the STOP process*, but the interval from presentation of the stop signal to successful interruption of response preparation must be occupied by at least two processes, one that encodes the stop signal and a subsequent one that interrupts response preparation to cancel the movement. Only the latter process should be identified

with a STOP process that directly influences response preparation. The more potent this terminal STOP process, then the briefer the interaction with the GO process and thus the more independent appear the finish times of GO and STOP.

Realizing that a complete response to the stop signal includes encoding, mapping and enacting provides insight into quantitative differences in SSRT observed across studies. Previous studies using acoustic stop signals and manual movements yielded SSRT values of around 200 msec (Logan 1994) while use of a fixation spot at a stop signal for saccades yields SSRT values around 100 msec (Hanes & Schall 1995). The difference in SSRT between the saccade and manual versions of the countermanding task probably derives from the fact that a visual stimulus flashing in the fovea directly activates the gaze-holding fixation system (Munoz & Wurtz 1993a), but more time is needed to interpret an acoustic stimulus as a signal to stop a limb movement.

Realizing that a complete response to the stop signal includes encoding, mapping, and enacting also provides a critical perspective on the validity of some of the arguments in support of the independence premise. It has been argued that the lack of a difference in the lateralized readiness potential (De Jong et al. 1990, van Boxtel et al. 2001) or the activity of movement and fixation neurons in frontal eye field and superior colliculus (Hanes et al. 1998, Paré & Hanes 2003) between noncanceled trials and trials with no stop signal is evidence in support of the independence premise. However, this reasoning is flawed on two counts. First, it confuses dynamics with finish times. Second, presence of the stop signal does not guarantee that the STOP process was active. In fact, fixation cells in frontal eye field and superior colliculus are not activated on noncanceled trials of the saccade countermanding task. If this modulation of gaze-holding fixation cells instantiates the STOP process, then the STOP process was not activated on noncanceled trials in this task. Therefore, this test of independence is invalid because the STOP process was not activated. In fact, the absence of modulation of fixation and movement neurons in noncanceled trials has been used to interpret the possible role of activity of neurons in the medial frontal lobe in monitoring errors and response conflict (Stuphorn et al. 2000, Ito et al. 2003).

EVALUATING LINKING PROPOSITIONS FOR THE PRODUCTION OF SACCADES

Three decades of research on the neural basis of saccade production has produced a wealth of information that should provide a basis to evaluate the family of relations linking neural events with the preparation and execution of saccades.

Do Identical Neural States Map onto Identical Saccades?

The foregoing discussion indicates that "identical neural state" means "statistically indistinguishable state of a particular population of neurons with connections

appropriate to mediate the hypothesized function." What does "identical saccade" mean? Saccades can be identical according to endpoint, amplitude, and velocity, although saccades exhibit a stereotyped relation between amplitude and velocity (Becker 1989).

Much evidence supports this proposition for saccade execution. A very high correlation exists between saccade metrics and dynamics and the discharge rate of individual oculomotor, burst, and tonic neurons, but there is definite variability in the activity of single neurons associated with saccades of a given direction and amplitude (e.g., Sylvestre & Cullen 1999). However, it seems clear that the innervation that moves and holds the eyes is the result of a population of neurons with less collective variability. Differences in the pattern and degree of burst, tonic, and motor neuron discharge translate immediately into different muscle contractions and so to different eye movements.

Microstimulation of a given site in superior colliculus or frontal eye field evokes saccades of a particular direction and amplitude, and the variation in the endpoint of the saccade evoked by electrical stimulation is less than that for visually guided saccades (Bruce et al. 1985, van Opstal et al. 1990). Likewise, when saccades of different directions and amplitudes are made, the spatial distribution of activation in the superior colliculus and frontal eye field shifts accordingly. While the endpoints of repetitive saccades exhibit some scatter, the quantitative characteristics of this scatter suggest that it originates in random variation of activation within the motor map of superior colliculus (van Opstal & van Gisbergen 1989).

The identity between the timing of neural discharge and the initiation of a saccade entails certain complexities. First, the original analyses measured the threshold as the mean discharge rate across the sets of trials with particular reaction times. Obviously, the functional threshold cannot be the average because on all trials with activity less than the average, no saccade should be produced, and it is not clear how the nervous system could calculate the average. Moreover, the activity of any single neuron may be sufficient to predict reaction time with reasonable reliability (Hanes et al. 1998), but the collective activity of many neurons is necessary to produce saccades (e.g., Schiller & Chou 2000). A more reasonable hypothesis is that the threshold is some minimum value of activation across a pool of neurons. The value of this minimum and the size of this pool can be estimated from data collected in the countermanding task which afford a more quantitative statement of this proposition—the probability of generating a saccade given that a stop signal occurred is equal to the probability that the activity of the relevant neurons reaches the threshold. Current evidence indicates that a pool of around 10 movement neurons in frontal eye field provide activity of sufficient reliability to instantiate such a threshold (Brown et al. 2001).

However, exceptions to the hypothesis of a fixed threshold for evoking saccades have been observed. First, the magnitude of activity of movements cells in superior colliculus and frontal eye field before antisaccades is systematically less than that before prosaccades (Everling & Munoz 2000). However, this difference may be related to differences in the metrics and dynamics of antisaccades. Second, another

experiment recorded neural activity in one frontal eye field while electrically stimulating the contralateral frontal eye field to evoke saccades (Schlag et al. 1998). Stimulation of the contralateral frontal eye field could produce an identical burst of action potentials in certain frontal eye field neurons whether or not a saccade was evoked. Further research is needed to determine the generality of these exceptions.

Despite these qualifications, it seems clear that indistinguishable neural states do map onto indistinguishable saccade metrics, dynamics, and initiation time.

Do Identical Saccades Map onto Identical Neural States?

Several lines of evidence demonstrate that the same saccade can originate from markedly different brain states. For example, a saccade of a given vector can be evoked by electrical stimulation of a particular site in the superior colliculus or frontal eye field. But the same saccade can be evoked by simultaneous stimulation of two different sites such that the resulting saccade is the vector average of the pair of respective saccades (Robinson 1972). Likewise, a recent study has shown that a given saccade can occur under one circumstance following the activation of a pool of neurons in the superior colliculus responding to a single stimulus and under another circumstance following the activation of two pools of neurons responding to two stimuli presented simultaneously (Edelman & Keller 1998). This dissociation has been referred to as a motomere (Sparks 1999), in parallel with perceptual metemeres that are physically distinct stimuli that evoke indistinguishable perceptual reports (e.g., Ratcliff & Sirovich 1978). The existence of perceptual metemeres presents at once an opportunity and a barrier to describing how perceptual reports relate to neural states because they demonstrate a many-to-one mapping of brain states onto perception.

The fact that physically different stimuli cannot be distinguished perceptually means that somewhere between the receptors and the bridge locus information was lost. The existence of motomere equivalence classes has somewhat different implications. First, given that saccades are produced ultimately by a network in the brainstem, the pattern of activation in this network must bear a much more direct correspondence to the saccade that is produced. Consequently, ambiguity inherent in the pattern of activation in the superior colliculus and frontal eye field must be resolved in the brainstem to produce one particular saccade.

Second, evidence for many-to-one mapping of brain states onto movements has important implications for the neural basis of intentional actions. If the mapping of neural activity onto movement were one-to-one, then the causal basis of movements would be clear—a particular action follows necessarily from a given brain state as reliably as a reflex. While such an automatic causal process seems an adequate account of certain kinds of movements (e.g., blinks), it cannot provide a satisfactory account of other kinds of movements (e.g., winks). Intended movements are owned ("I did") while unintended movements are not ("It happened"). In other words, we can distinguish the *cause of* from the *reason for* movements (Davidson 1963).

In fact, some have argued that a many-to-one mapping of neural activity onto cognition and behavior provides room for intentional reasons within neural causes (Juarrero 1999). If a given saccade can be the realization of different brain states, then according to the argument, the dependence of the behavior on an intention holds in virtue of the content of the representation of the intention and not its neural realization as such (van Gulick 1993, Dretske 1998, Kim 1998). The relevant content answers, "Why did you do that?" Thus, the argument goes, a movement can be called an intentional action if and only if it originates from a cognitive state with meaningful content, and this content defines the cognitive state's causal influence.

We can apply this argument to saccades. The same saccade can be the outcome of two (or more) distinguishable patterns of neural activity instantiating two (or more) distinguishable representations. The representation of a single focus of activation in the superior colliculus leading to a saccade of a particular vector can be distinguished from the representation of two foci of activation leading to the same saccade through averaging. However, the two mappings of neural representations onto saccades do not have equal status. Averaging saccades are maladaptive, for they direct gaze to neither stimulus; they are errors that must be corrected to achieve the goal of vision. According to this analysis, averaging saccades would be regarded as unintentional errors. If asked, subjects would typically report that they did not intend to shift gaze into the space between two stimuli. In contrast, an accurate saccade to one of the two stimuli would achieve the goal of vision and would more likely be owned as intentional.

This analysis depends on whether the brain can represent the consequences of actions. Does the brain know what it means to do? Recent research has shown that the medial frontal lobe registers errors and success (e.g., Botvinick et al. 2001, Blakemore et al. 2002, Schall et al. 2002). For example, in monkeys performing the countermanding saccade task neurons signaling errors were observed in the supplementary eye field (Stuphorn et al. 2000) and anterior cingulate cortex (Ito et al. 2003). Many of these neurons responded as well to omission of earned reinforcement. Such signals can be used to adjust behavior and provide the basis for distinguishing "I did" from "It happened."

SUMMARY AND CONCLUSIONS

The current literature in cognitive neuroscience includes many claims identifying certain neural events (usually activation of neurons in some part of the brain) with particular cognitive capacities (often multifaceted such as decision making, memory, or even social cooperation). This review has examined the conceptual and technical complexity of formulating and evaluating such claims in the domain of saccadic eye movements. Much is at stake in this endeavor in view of the ethical and legal ramifications of determining the nature of the mapping between mental states and brain states (Farah 2002, Moreno 2003). But, if the relationship between neural events and control of gaze is so difficult to elucidate, what hope

have we of understanding the mechanisms of more elaborate cognitive processes? Despite fantastic technical developments, lingering methodological and conceptual limitations hinder progress in understanding how mental processes (wrapped up in folk psychology) reduce to or emerge from neural processes. Will we understand how "I do" even though I don't, like we understand how the "sun rises" even though it doesn't?

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