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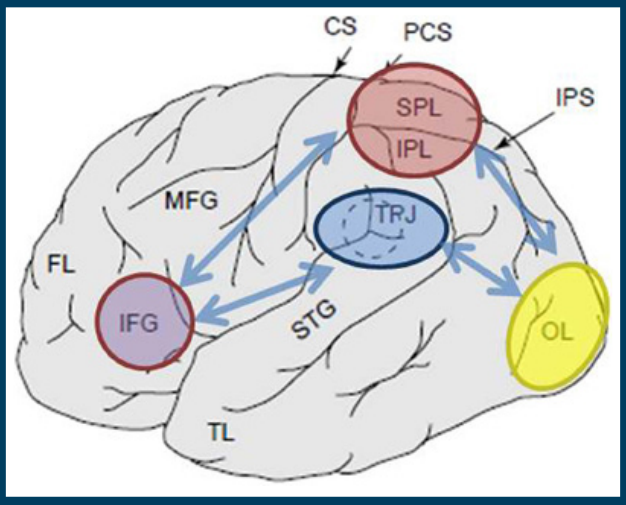

COGNITIVE FUNCTIONS OF THE POSTERIOR PARIETAL CORTEX

Topic Editors
Christos Constantinidis, David J. Bucci and Michael Rugg

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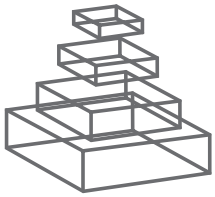

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COGNITIVE FUNCTIONS OF THE POSTERIOR PARIETAL CORTEX

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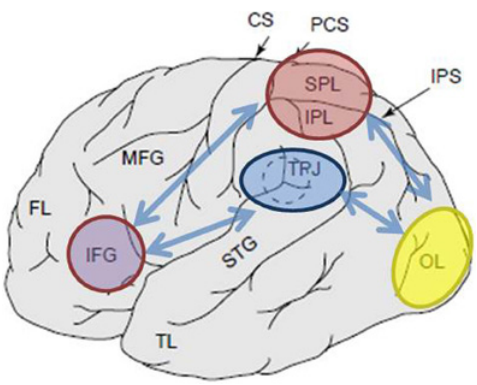

Schematic depiction of the lateral surface of the human brain, with parietal areas subserving attentional orienting highlighted. From Shomstein, 2012 in this e-Book.

The Posterior Parietal Cortex has been traditionally associated with visuo-spatial perception however recent work indicates its involvement in wide range of cognitive functions. The Research Topic will examine the role of the Posterior Parietal Cortex in cognitive functions such as learning, working- and long-term memory, decision-making, numbering, categorization, planning, and reward. It will seek to bridge work on human, monkey, and rodent Posterior Parietal Cortex and address the homology and correspondence between human and animal models. Results from anatomical, lesion, neurophysiological, functional imaging, and transcranial magnetic stimulation will be included. The issue will seek to present viewpoints on current areas under debate and highlight consensus on questions that have reached broad agreement. The unique and shared functions of the Posterior Parietal Cortex compared to other brain areas will also be addressed. Contributions will include Original Articles, as well as Reviews, Theories, and Hypotheses. We expect that these contributions will provide a primer of the current state of knowledge, identify unresolved questions, highlight recent conceptual and methodological advances, and stimulate future research.

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EDITORIAL
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Cognitive functions of the posterior parietal cortex

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The posterior parietal cortex has traditionally been associated with visuo-spatial perception and spatial attention, however, accumulating evidence indicates that it is involved in a much wider range of cognitive functions. The articles included in the E-book review experimental data and theoretical considerations, as well as reviews of recent work supporting this idea. Anatomical, lesion, neurophysiological, and functional imaging data are discussed. Animal models (rodent and primate) as well as human studies are covered. Finally, the unique and shared functions of the posterior parietal cortex are compared to other brain areas. These contributions provide a primer of the current state of knowledge, identify unresolved questions, highlight recent conceptual and methodological advances, and, we hope, will stimulate future research.

In the first part of the E-book, evidence from rodent model systems is presented. Articles examine the contribution of animal models to long-term memory (Myskiw and Izquierdo, 2012), illusory conjunctions (Kesner, 2012), ranking of topographic signals (Broussard, 2012), and relational learning (Robinson and Bucci, 2012). A common theme across these topics is the intersection of attentional functions of posterior parietal cortex with learning/memory-related processes. Data are presented from studies that combine experimental lesion techniques and electrophysiological methods with sophisticated behavioral assays that attempt to elucidate the precise contributions of posterior parietal cortex.

A series of experiments in non-human primate models similarly reveal activation of the posterior parietal cortex in a variety of cognitive functions, such as numerosity (Roitman et al., 2012), categorization (Fitzgerald et al., 2012), and decision-making (Huk and Meister, 2012). Spatial signals are present and shape peri-personal shape and limb movements (Hadjidimitrakis et al., 2012), however, spatial information also forms an abstract spatial representation that can be decoupled from sensorimotor control (Chafee and Crowe, 2012). Neurophysiological experiments provide insights on the nature of differences between the posterior parietal cortex and other cortical areas, such as the prefrontal cortex, in the context of visual search (Wardak et al., 2012) and other tasks (Katsuki and Constantinidis, 2012). The conclusion that emerges from these studies is that the posterior parietal cortex is activated in a wide range of tasks, and individual parietal neurons exhibit neural correlates of complex cognitive functions.

In the last part of the E-book, evidence from human studies is considered. Imaging studies routinely reveal BOLD activation during episodic memory tasks (Berryhill, 2012; Levy, 2012). In recent years, nuanced memory deficits following parietal lesions have also been recognized (Berryhill, 2012). EEG and MEG studies have yielded consistent evidence about the time course of parietal mnemonic activation (Levy, 2012). Both process- and content-based models have been proposed to account for the nature of this activation (Berryhill, 2012; Levy, 2012). Finally, the posterior parietal cortex has been implicated in cognitive control, with different subdivisions proposed to be specialized for bottom-up and top-down control (Shomstein, 2012).

Collectively, these studies illustrate our current understanding of the posterior parietal cortex with regard to cognitive operations. While the nature and extent of its involvement continues to be investigated, it is now clear that its role goes beyond the functions traditionally ascribed to it, spatial representation and attention—a major development of the past few years.

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REVIEW ARTICLE
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Posterior parietal cortex and long-term memory: some data from laboratory animals

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The posterior parietal cortex (PPC) was long viewed as just involved in the perception of spatial relationships between the body and its surroundings and of movements related to them. In recent years the PPC has been shown to participate in many other cognitive processes, among which working memory and the consolidation and retrieval of episodic memory. The neurotransmitter and other molecular processes involved have been determined to a degree in rodents. More research will no doubt determine the extent to which these findings can be extrapolated to primates, including humans. In these there appears to be a paradox: imaging studies strongly suggest an important participation of the PPC in episodic memory, whereas lesion studies are much less suggestive, let alone conclusive. The data on the participation of the PPC in episodic memory so far do not permit any conclusion as to what aspect of consolidation and retrieval it handles in addition to those dealt with by the hippocampus and basolateral amygdala, if any.

Keywords: posterior parietal cortex, memory consolidation, memory retrieval, episodic memory, working memory

INTRODUCTION

The posterior parietal cortex (PPC) is involved in a variety of mental and neural processes, as other articles in this issue attest. In recent years, it was found to play a key role both in working memory, and in the making and retrieval of episodic memory. The role of the PPC in memory was viewed as untraditional by Olson and Berryhill in 2009.

WORKING MEMORY

There is strong and variegated evidence for a role of the PPC in working memory (see other articles in this volume). Most authors propose a role [e.g., (Rawley and Constantinidis, 2009)], as part of an extensive working memory brain circuit that involves dopaminergic mechanisms in regions of the prefrontal cortex (Goldman-Rakic, 1991; Izquierdo et al., 1998) and hippocampus (Izquierdo et al., 1998; Aujla and Beninger, 2001) and cholinergic muscarinic (Ingles et al., 1993; Izquierdo et al., 1998), and nicotinic receptors in the basolateral amygdala (Barros et al., 2005). Actually there are many types of working memory: for example, in music, working memory for melody activates the PPC whereas working memory for rhythm activates the cerebellum and the right insula (Jerde et al., 2011), and the prefrontal and PPC contributions to spatial working memory are different (Curtis, 2006). The role of the PPC in working and long-term memory of spatial tasks is differentially affected by reversible inhibition of the PPC by the local infusion of lidocaine (Espina-Marchant et al., 2009).

Working memory is used both in order to make and to retrieve memories. It is well-known to fail in schizophrenia (Lepage et al., 2010; Kang et al., 2011) and to decline with old age (Elliott and Dolan, 1998) along with the development of an asymmetry of parietal cortex activation (Otsuka et al., 2008).

There have been several important functional studies of working memory in animal models in recent years. Very few studies have tested effects of drugs on working memory given by microinjection into the PPC in rats or mice (Izquierdo et al., 1998), as is usually done in investigations of the role of other brain regions in this type of memory, or any other for that matter (Izquierdo et al., 2006, 2007). Our group has reported on the effect of well-known neurotransmitter antagonists on working memory measured as immediate memory in the rat (Izquierdo et al., 1998). Immediate memory is recognized as a measure of working memory (Goldman-Rakic, 1991; see Jacobsen, 1936).

In the study reviewed here (Izquierdo et al., 1998), rats were implanted with chronic bilateral cannulae in the hippocampus, entorhinal, anterolateral prefrontal, or PPC and were submitted to a one-trial step-down inhibitory avoidance task, by far the task most widely used task in memory studies over the past 60 or so years (McGaugh, 1966, 2000; Gold, 1986; Izquierdo et al., 2007). The animals were given various treatments (the cholinergic muscarinic receptor blocker, scopolamine 2.5 μg, the glutamate NMDA antagonist, aminophosphonopentanoic acid (AP5) 5 μg, the glutamate AMPA receptor antagonist, CNQX 0.5 μg, the $GABA_A$ receptor agonist muscimol 0.5 μg, or the dopamine D1 receptor antagonist, SCH233900, 0.5 μg) into the structures reached by the cannulae 5 min before training. The doses were those usual in brain microinjection studies [see (Izquierdo et al., 1998, 2007) for references]. During training, the animals were gently placed on a 3 cm-high, 25 cm-long platform facing a metallic grid and left to explore the apparatus freely. In 5–15 s all of them eventually stepped down onto the grid. When they had placed their four paws on it, they received a mild (0.3 mA), very brief (2 s) footshock, were immediately withdrawn from the apparatus, and were placed again on the platform, a procedure that

took less than 5 s. Their step-down latency was measured again, as an estimation of immediate (working) memory. The drugs were given 5 min before training. They had different effects in the different structures; all except AP5 were able to markedly inhibit immediate memory when given into PPC or hippocampus, suggesting that muscarinic cholinergic receptors, dopamine D1 receptors, and AMPA but not NMDA glutamate receptors play a role in working memory in these two areas (Izquierdo et al., 1998). The D1 antagonist studied was SCH23390, the AMPA receptor antagonist was CNQX, and the NMDA blocker was AP5. In the anterolateral prefrontal cortex, long known to play a role in working memory (Goldman-Rakic, 1991; Izquierdo et al., 1998), SCH23390 also hindered working memory. The data suggest that the PPC is involved in the processing of working memory, measured as immediate memory, through biochemical processes not very different from those used by other brain structures traditionally known to regulate that form of memory, like anterolateral prefrontal cortex, hippocampus, and amygdala (Goldman-Rakic, 1991; Izquierdo et al., 1998, 2007; Aujla and Beninger, 2001). In the posterior parietal area these processes apparently involve glutamate AMPA but not NMDA glutamate receptors, D1 dopaminergic enhancement, and GABAergic down regulation.

As mentioned, probably the PPC plays its role in working memory in connection with that of the hippocampus (Izquierdo et al., 1998; Aujla and Beninger, 2001) and basolateral amygdala (Ingles et al., 1993; Barros et al., 2005), two structures to which it is linked by afferent and efferent pathways that relay in the entorhinal cortex (Ding et al., 2000; Izquierdo et al., 2006).

A number of studies, particularly lesion studies (Pinto-Hamuy et al., 2004; Espina-Marchant et al., 2009; McVea and Pearson, 2009) have shown a role of the PPC in the long-term consequences of working memory. Since the lesions antecede the behavioral procedures it is difficult to conclude whether their deleterious effect is on the working memory itself or on its transfer to short- or long-term memory stores. In electrophysiological studies on the firing of posterior parietal cells during the walking of cats through obstacles (McVea and Pearson, 2009; McVea et al., 2009), the information thus generated can then be kept during minutes for on-going walking (McVea et al., 2009) or for much longer times, when walking again through that path much later (McVea and Pearson, 2009). Such long-lasting transfers of working memory information must participate in the engagement of the PPC with the hippocampus in the learning of spatial navigation (Whitlock et al., 2008) or ambulation (McVea et al., 2009), whose memory can of course last for many days or more.

Constantinidis and his associates (Constantinidis, 2006; Curtis, 2006; Joelving et al., 2007; Rawley and Constantinidis, 2009) have studied extensively the firing of PPC neurons in situations that clearly (Constantinidis and Steinmetz, 1996) or most likely (Curtis, 2006; Joelving et al., 2007) involve working memory. Among their many key findings, one is particularly intriguing: the decreased range in the 5–10 Hz frequency range of such firing during presentations of visual stimuli in a working memory situation relative to control periods (Curtis, 2006). This probably resulted from the longer refractory periods in the former and engagement of local inhibitory circuitry; as the authors say, this has also been observed in prefrontal regions that are involved in working memory processing. For other relation between prefrontal and parietal participations in this processing, [see (Quintana and Fuster, 1999; Chafee and Goldman-Rakic, 2000; Curtis, 2006)].

A number of authors suggest that the PPC, long known to be crucially involved in attention (Constantinidis, 2006; Bucci, 2009), is in reality an interface between attention and learning (Bucci, 2009), and/or part of a larger network involved in attention which includes the dorsocentral striatum, the lateral posterior indeed thalamic nucleus and other brain regions (Reep and Corwin, 2009). The distinction between the mechanisms of attention and working memory is subtle (Constantinidis, 2006; Bucci, 2009; Reep and Corwin, 2009), and probably both are different depending on the part of the brain examined. For example, recording experiments in monkeys show that attention is processed by signals derived from task demands ("top-down") in the prefrontal cortex, but by signals from salient stimuli ("bottom-up") in the parietal cortex (Buschman and Miller, 2007). There have been studies and speculations on the intersection of attention and memory, which suggest that the PPC may serve to filter distractors (Friedman-Hill et al., 2003) and maintains or shifts internal attention among the representation of items in working memory (Berryhill et al., 2011).

LONG-TERM MEMORY: ENCODING AND/OR CONSOLIDATION

Encoding is the first step in creating a memory. It involves the perception of sensory signals and their after effects. Immediately thereafter there is consolidation, which consists of the translation of those perceptions into brain language [postsynaptic transmitter effects and action potentials] (Delgado-García, 2011) and their formatting into memory files. Memory is a brain function that comprises encoding, consolidation, persistence, maintenance, and retrieval.

Participation of the PPC in long-term episodic memory began to be realized rather recently and has so far been specifically studied by few groups (Rogers and Kesner, 2007; Berryhill et al., 2007, 2010a,b; Keene and Bucci, 2008; Hutchinson et al., 2009; Drowos et al., 2010). Some of this work has involved classic animal (Compton et al., 1994; Rogers and Kesner, 2007; Berryhill et al., 2007; Keene and Bucci, 2008) or human (Berryhill et al., 2010a,b; Drowos et al., 2010) lesion studies, and typical post-training microinjection and assay techniques (Zanatta et al., 1996; Ardenghi et al., 1997; Izquierdo et al., 1997; Barros et al., 1998; Schröder et al., 2000; Luft et al., 2004; Bonini et al., 2005; Alonso et al., 2005) or post-training lesion studies (Rossato et al., 2004).

The formation of long-term episodic memories is not to be confused with the transfer of working memory to long-term stores (Richmond et al., 2011). The former relies on a complex sequence of biochemical events in the hippocampus (Izquierdo et al., 2007) that are linked to, and probably involve long-term potentiation (Delgado-García and Gruart, 2006; Whitlock et al., 2006, 2008; Clarke et al., 2010); related but different changes occur in basolateral amygdala, entorhinal cortex, and PPC (Jiménez-Díaz et al., 2006; Izquierdo et al., 2007). The transfer of working memory to long-term stores uses as yet unknown

mechanisms that probably occur mainly in the PPC and may maintain or shift the representation of items in working memory (Berryhill et al., 2011).

The contribution of the parietal cortex to episodic memory in higher primates including humans is viewed by many as a puzzle (Cabeza et al., 2008): whereas an activation of this region is frequently seen in functional neuroimaging studies of episodic memory, parietal lesions in primates including man do not normally cause episodic memory deficits (Cabeza et al., 2008; Schoo et al., 2011). If the PPC is viewed as part of complex circuits that mediate consolidation (Izquierdo and Medina, 1997; Izquierdo et al., 1997, 2006) and retrieval (Izquierdo et al., 1997; Barros et al., 2000, 2001), the "puzzle" might be explained by the possibility that other regions of the brain take over the role of the PPC in consolidation and retrieval, or by the probability that the role of the PPC in both processes is accessory rather than central (Izquierdo et al., 1997, 2006). In rats, pharmacological inactivation (Pinto-Hamuy et al., 2004; Espina-Marchant et al., 2009) of the PPC or inhibitors of protein kinases A (Zanatta et al., 1996; Ardenghi et al., 1997; Izquierdo et al., 1997; Barros et al., 1998), protein kinase C (Bonini et al., 2005) or of extracellularly regulated kinases (ERKs), or a glutamatergic NMDA receptor blocker or a GABA-A agonist given into the PPC have strong post-training amnesic effects (Alonso et al., 2005). Post-training lesions of the PPC, unlike those produced in the hippocampus, are amnesic for idiothetic information memory in the rat (Okaichi et al., 2006). It is to be noted, however, that unlike in the hippocampus or the amygdala (Cammarota et al., 2008) in the parietal cortex these amnesic effects are obtained with delayed (i.e., > 90 min) rather than with immediate post-training administrations (Zanatta et al., 1996; Izquierdo et al., 1997). This has been attributed to a delay caused by the entorhinal cortex station between hippocampus and/or amygdala and parietal cortex (Izquierdo et al., 1997, 2007); indeed the drug effects are seen when the drug treatments are given 30 min post-training in the entorhinal cortex (Izquierdo et al., 1997), and 90 or 180 min but not 0–60 min post-training in the PPC (Rossato et al., 2004). Treatments that stimulate protein kinases given into the PPC enhance episodic retrieval when given 90 min post-training (Ardenghi et al., 1997); so does the indirect $GABA_A$ receptor antagonist, bicuculline (Luft et al., 2004).

Thus, some of the molecular components of the role of the PPC in memory encoding or consolidation have been identified by pharmacological means; i.e., by the microinfusion of a variety of drugs into this structure bilaterally at various times in the post-training period (Ardenghi et al., 1997; Izquierdo et al., 1997; Barros et al., 1998; Schröder et al., 2000; Luft et al., 2004; Alonso et al., 2005; Bonini et al., 2005); others by measuring biochemical changes in this structure at those times (Alonso et al., 2005; Izquierdo et al., 2007). They were found to participate, as said, beginning 60–90 min post-training, i.e., 60–90 min after the participation of the hippocampus and the basolateral amygdala in consolidation, and 30 or so min after that of the entorhinal cortex (Izquierdo and Medina, 1997; Izquierdo et al., 2006).

When infused into the PPC 1 h after training, recombinant BDNF (brain-derived neurotrophic factor) increased, and an antibody against BDNF decreased, both short- and long-term memory of one-trial inhibitory avoidance, and pCREB/CREB levels in that structure. The effects of BDNF or its antibody did not correlate with changes in local activity of ERK1, ERK2, or PKA, which suggests they were not mediated by changes in the activity of these enzymes (Alonso et al., 2005). These results are of importance since BDNF is known to stimulate growth of recently stimulated synapses (Nagappan and Lu, 2005) and because of this has been attributed role in consolidation (Alonso et al., 2002) and post-consolidational mechanisms favoring memory persistence (Bekinschtein et al., 2007). They enhance the postulation of PPC as a brain region crucial for memory formation (Alonso et al., 2005).

It is yet not known just in what aspects or components of episodic memory formation the PPC is involved or plays a role. Bilateral damage to this area does not impair associative memory for paired stimuli, which suggests it should be involved not in the Pavlovian association but in other aspects of episodic memory (Berryhill et al., 2010a). Some studies suggest a role in the emotional component (Weymar et al., 2011), which, as is known, is at the root of memory persistence (McGaugh, 2000; Izquierdo et al., 2007) and in humans at least is widely believed to be always present to some degree. Others suggest a role in attentional components (Sestieri et al., 2011) which may be important in encoding or consolidation. In all likelihood, whatever the role, the PPC probably does not play it alone, but in association with complex circuits including the hippocampus, amygdala, entorhinal cortex (Izquierdo et al., 2007) and prefrontal regions (Sohn et al., 2005). In contrast to several other structures that are involved in consolidation, such as the hippocampus, basolateral amygdala, entorhinal, and at least parts of the prefrontal cortex [recent negative pharmacological findings suggest that the PPC is not involved in extinction] (Myskiw et al., 2010).

Kesner and associates (Chiba et al., 2002) studied two variants of a continuous recognition procedure in rats, a continuous reinforcement condition reflecting perceptual memory and a differential reinforcement condition reflecting episodic-like memory in a 12-arm radial maze. [For a discussion on what is episodic memory in rats, see (Kart-Teke et al., 2006)]. They showed a double dissociation between the parietal cortex, whose lesions impair performance in the continuous (perceptual) condition but not in the episodic-like situation, and the hippocampus whose lesions caused just the opposite. These findings are at odds with the relatively large literature from our group on the similar effects of amnesic treatments given into the hippocampus or the PPC in episodic memory measured in a one-trial avoidance task in rats. Certainly the type of task and the motivational and perceptual aspects involved could play a major role in lesion or drug effects; but the one-trial avoidance task is no doubt acquired and retrieved through episodes, and it has biochemical/electrophysiological correlates in hippocampus that are very similar to those of other aversive (Izquierdo et al., 2006; Whitlock et al., 2006) or non-aversive tasks which are clearly episodic in nature (Clarke et al., 2010) and, save for the differences in time-course, similar to those that may be described for the PPC [see above and (Izquierdo et al., 1997, 2007)]. In another study, Kesner and his coworkers suggested that whereas the hippocampus is necessary for

metric representations, the parietal cortex would be necessary for topological representations (Goodrich-Hunsaker et al., 2005; see Kesner, 2009).

The interplay of the PPC and the main areas that underlie memory, such as the hippocampus (Izquierdo et al., 2007) involves probably a very wide variety of processes and functions mediated by relays in the entorhinal cortex and connections with other cortical and non-cortical regions (McCormick et al., 2010). Some of the interactions involve the action of hormones or other substances on both the hippocampus and the parietal cortex, of which 11-beta-hydroxysteroids like glucocorticoids may be an example: a dehydrogenase for such substances is expressed in both brain regions and increases with aging (Holmes et al., 2010). Glucocorticoids modulate a variety of memory-related processes (Schwabe and Wolf, 2011).

The participation of the PPC in memory consolidation long after the hippocampus and the basolateral amygdala have done so may represent a final, but perhaps not indispensable, "approval signature" on the whole process initiated by the hippocampus and the amygdala (Izquierdo et al., 2006).

RETRIEVAL OF LONG-TERM MEMORY

Many studies suggest that the PPC regulates retrieval and others that it is specifically in charge of recognition (Rugg and Curran, 2007; Haramati et al., 2008; Weiss et al., 2009; Winters and Reid, 2010; Weymar et al., 2011). Retrieval is supposed to englobe both recall and recognition. Many view the dichotomy between recall and recognition as flimsy [see (Olson and Berryhill, 2009)]. In many behaviors one cannot see one without the other. Even in animal tasks defined as recognition tasks (object recognition, social recognition) there must be recall prior to or together with recognition; if characteristics of the recognized object are not recalled there can be no recognition. The word "recognition" means "cognition again" or "renewed cognition"; i.e., "to know again." In order to "call again" (recall) a memory, animals must "know" what they are calling. However, there can be of course recall without recognition: animals may "remember" without really knowing what they remember.

Recognition is believed to result from two processes: recollection and familiarity (Weymar et al., 2010). Evoked potential and other studies suggest that the hippocampus and parietal cortex are involved with the former and the prefrontal cortex and amygdala are involved with the latter (Rugg and Curran, 2007; Farovik et al., 2011; Weymar et al., 2011). The recollection process can be inhibited by systemic propranolol in humans (Weymar et al., 2011) and declines with age (Friedman et al., 2010).

It has been known for a long time that retrieval is not a passive process, but rather one that requires active construction (Barros et al., 2000; Flavell et al., 2011). Several molecular events are recruited at a short notice in a number of brain areas, mostly cortical, and are required for retrieval, including recall and recognition; some of these events are similar to those of consolidation, but their time-course is compressed into a few seconds, rather than distributed over hours (Barros et al., 2000, 2001; Szapiro et al., 2000).

In any case, clearly the PPC participates in the retrieval of one-trial inhibitory avoidance. The localized bilateral infusion of the dopamine D1 agonist SKF38393, noradrenaline, the 5HT-1A antagonist NAN-190, or of the muscarinic stimulant oxotremorine into the PPC 0 min prior to a 24 h retention test session of one-trial step-down inhibitory avoidance enhances retention test performance. The localized bilateral infusion of the D1 antagonist SCH23390, of the β-noradrenergic antagonist timolol, of the 5HT-1A agonist 8-HO-DPAT (hydroxyldipropylaminotetraline) and of the muscarinic antagonist scopolamine hinders retention test performance. Three hours after the infusions, retention test performance returned to normal in all cases. None of these treatments affected locomotion or rearing in an open field or behavior in the elevated plus maze. Therefore, their effects on retention testing can be attributed to an influence on one or other or all components of retrieval. In conclusion, memory retrieval of this apparently simple task requires the participation of CA1, entorhinal, posterior parietal and anterior cingulate cortex, and is strongly modulated by, dopaminergic D1, β-noradrenergic, muscarinic cholinergic, and 5HT1A receptors in the four areas. The first three types of receptor enhance, and the latter inhibits, retrieval (Barros et al., 2001). In addition, the glutamate NMDA receptor blocker, AP5, the AMPA receptor blocker, 6,7-dinitroquinoxaline-2,3 (1H,4H) dione (DNQX), and various glutamate metabotropic receptor antagonists also block retrieval when infused into the PPC (Barros et al., 2000; Szapiro et al., 2000).

Concerning the molecular mechanisms involved in retrieval beyond the receptor level in the PPC, infusion into that structure 5 min before retention testing of the ERK inhibitor PD098050, or of the inhibitor of the cAMP-dependent protein kinase (PKA), Rp-cAMPs inhibit retrieval, whereas infusion of the PKA stimulant, Sp-cAMPs enhances retrieval of the inhibitory avoidance task (Barros et al., 2000; Szapiro et al., 2000). All these drugs, at the same doses, had been previously found to alter long-term memory formation of this task.

PPC AND MEMORY: OVERVIEW

Data suggest a key role of the PPC in working memory of various types, alongside and possible in cooperation with that of the anterolateral prefrontal cortex and hippocampus, and involving different neurotransmitter combinations than those in these other structures. In addition, the PPC also plays an important and necessary role in the memory consolidation of at least one-trial inhibitory avoidance. This role is exerted 90–180 min after that of the hippocampus and basolateral amygdala, and requires more or less the same molecular processes used by these two other regions: glutamatergic transmission down regulated by $GABA_A$ synapses, and activation of the ERKS and the protein kinases A and C. At the time of retrieval, the PPC is required alongside the hippocampus, basolateral amygdala, entorhinal cortex, and anterior cingulate cortex. It requires, like these other structures, unimpeded ERK and PKA function, and is regulated positively by β-noradrenergic, D1-dopaminergic, and muscarinic cholinergic receptors, and down regulated by serotonin-1A synapses. Therefore, the PPC may be viewed as an important member of the neural networks that govern working memory and the formation and retrieval of episodic memory.

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Parietal lesions produce illusory conjunction errors in rats

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When several different objects are presented, visual objects are perceived correctly only if their features are identified and then bound together. Illusory-conjunction errors result when an object is correctly identified but is combined incorrectly. The parietal cortex (PC) has been shown repeatedly to play an important role in feature binding. The present study builds on a series of recent studies that have made use of visual search paradigms to elucidate the neural system involved in feature binding. This experiment attempts to define the role the PC plays in binding the properties of a visual object that varies on the features of color and size in rats. Rats with PC lesions or control surgery were exposed to three blocks of 20 trials administered over a 1-week period, with each block containing 10-one feature and 10-two feature trials. The target object consisted of one color object (e.g., black and white) and one size object (e.g., short and tall). Of the 10 one feature trials, five of the trials were tailored specifically for size discrimination and five for color discrimination. In the two-feature condition, the animal was required to locate the targeted object among four objects with two objects differing in size and two objects differing in color. The results showed that the PC lesioned compared to control rats had difficulty in learning the one and two features components of the task and the rats also performed more poorly on the one vs. two feature components of the task. Based on a subsequent error analysis for color and size, the results showed a significant increase in illusory conjunction errors for the PC lesioned rats relative to controls for color and relative to color discrimination, suggesting that the PC may support feature binding as it relates to color. There was an increase in illusory conjunctions errors for both the PC lesioned and control animals for size, but this appeared to be due to highly variable performance with size discrimination. Overall these results suggest that the PC rats display performance errors that appear to be consistent with the notion of illusory conjunction errors.

Keywords: illusory conjunctions, parietal cortex, rats

INTRODUCTION

It has been suggested that the parietal cortex (PC) may play an important role in binding features of objects, objects, and places, as well as egocentric and allocentric spatial processing. There are data with rodents that support a role for the PC in cross-modal, as well as egocentric and allocentric spatial processing (Long et al., 1998; Rogers and Kesner, 2007), but there are no data that have assessed the role of the PC in rodents on binding of object features. Treisman (1998) suggested that the binding of different features of objects may involve using spatial attention to locations to aid in the selection of various features that are currently active in the same location, while suppressing features from other locations to prevent erroneous binding. Furthermore, the PC may play a very important role in ensuring that illusory conjunction errors do not appear in a variety of tasks including search tasks. Thus, the PC may be directly involved in perceptual binding between, for example, a shape and a color or a shape and a size requiring spatial attention. Support for this idea comes from the performance of patient RM with bilateral PC damage, who had difficulty in tasks requiring binding shape and color or shape and size. When shown two different colored letters, RM made many errors in the form of illusory conjunctions combining the shape of one letter with the color of the other (Friedman-Hill et al., 1995). Similarly, in a visual search task requiring the detection of a target based on the conjunction of two features, RM made many errors, but RM had no difficulty in detecting a target based on one feature (Robertson et al., 1997). The study was designed to develop an animal model of feature binding and determine whether PC lesions relative to sham lesions in rats result in the production of illusory conjunction errors using a visual search paradigm similar to the (Robertson et al., 1997) study with objects that varied either only on features of color or size (one feature) or the combination of color and size (two features).

MATERIALS AND METHODS

SUBJECTS

Eleven male Long–Evans rats initially weighing ∼350 g were used as subjects. At the beginning of the study, all rats were food-deprived to 80% of their free-feed weight and allowed access to water *ad libitum*. The rats were housed independently in standard plastic rodent cages and maintained on a 12-h light/dark cycle. All testing was conducted in the light portion of the light/dark cycle.

APPARATUS

A white cheese board served as the testing apparatus for the experiment. The surface of the apparatus stood 65 cm above the floor, was 119 cm in diameter, and was 3.5 cm in thickness. One-hundred and seventy-seven food wells (2.5 cm in diameter and 1.5 cm in depth) were drilled into surface of the round board in evenly spaced parallel rows and columns, which were 5 cm apart. The apparatus was kept in a well-lit room with no windows; one door, a chair, a small table, and posters on the walls served as distal spatial cues. A black start box (24 cm long, 15 cm wide, and 17 cm high) was constructed to house the rat between trials. The black box was positioned on top of the round board perpendicular to the rows and parallel to the columns with the posterior edge of the box at the edge of the cheeseboard. The box had a hinged top for easily transferring animals into and out of the box. The front of the box had a guillotine door that could only be raised and lowered by the experimenter. Stimuli were three-dimensional wooden block objects 2 cm in diameter that differed from each other in both color (black or white) and size (4 or 6 cm in height).

SHAPING

During the first week of training, rats were handled 15 min daily. During the second week of training, rats were introduced to the apparatus. Rats were given 15 min to explore the white cheese board. Froot Loops (Kellogg, Battle Creek, MI) were randomly distributed over the maze to induce exploration.

SURGERY

Rats were anesthetized with pentobarbital (Nembutal; 60 mg/kg i.p.). Each rat was placed in a stereotaxic apparatus (David Kopf Instruments) with an isothermal heating pad to maintain body temperature at 37°C. With its head level, the scalp was incised and retracted to expose bregma and lambda and positioned them in the same horizontal plane. PC lesions were made via aspiration. The lesions were 1 mm posterior to bregma to 4.5 mm posterior to bregma, 2 mm lateral to midline to approximately 1 mm above the rhinal sulcus in the medial-lateral plane, and 2 mm ventral to dura. Control lesions underwent the same procedure as the PC lesioned rats, except that no tissue was removed. Following surgery, the incisions were sutured and the rats were allowed to recover for one week before experimentation. They also received Children's Tylenol in water as an analgesic. All animal care and experimental procedures conformed to the National Institutes of Health and Institution for Animal Care and Use Committee guidelines for proper care and use of experimental animals.

ACQUISITION OF THE SEARCH TASK

Three blocks of 20 trials were administered over a 1-week period, and each block contained 10-one feature and 10-two feature trials. The target object consisted of one color object (e.g., black and white) or one size object (e.g., short and tall). Of the 10-one feature trials, five of the trials were tailored specifically for size discrimination and five for object discrimination. In the one-feature condition the subject was required to locate the targeted object among four other objects that differed in either color or height, i.e., if the target object was a small black block, then four small white blocks for the color condition, and four tall black blocks for the size condition would surround the object. In the two-feature condition, the animal was required to locate the targeted object among four objects with two objects differing in size and two objects differing in color. For both the one- and two-feature conditions, the target object for each animal was randomly predetermined and remained consistent throughout the experiment, whereas placing of the other objects varied on each trial. The rule to be learned in order to obtain a food reward was to discriminate between the size and colored objects in order to displace the targeted object. For each trial, the randomly targeted object covered a baited food-well in one of five randomly assigned spatial locations. The inter-trial interval was 30 s. The number of errors for each trial was recorded and the food reward was Froot Loops breakfast cereal (Kellogg's).

HISTOLOGY

At the end of the experiments, each rat was given a lethal intraperitoneal injection of sodium pentobarbital. The rat was perfused intracardially with 10% (wt/vol) formalin in 0.1 M phosphate buffer. The brain was then removed and stored in 30% (vol/vol) sucrose-formalin for one week. Transverse sections (24 μm) were cut with a cryostat through the lesioned area and stained with cresyl violet.

RESULTS

HISTOLOGY

The PC lesions extended from 1 mm posterior to bregma to 4.5 mm posterior to bregma, and 2 mm lateral to midline to approximately 1 mm above the rhinal sulcus in the medial-lateral plane (**Figure 1**). There was some sparing of the PPC at the ventrolateral aspect adjacent to the temporal association cortex (TeA) as well as some sparing between 1 and 2 mm lateral to midline. The PC lesions generally did not result in damage to the dorsal or ventral hippocampus, fimbria/fornix, or temporal cortices.

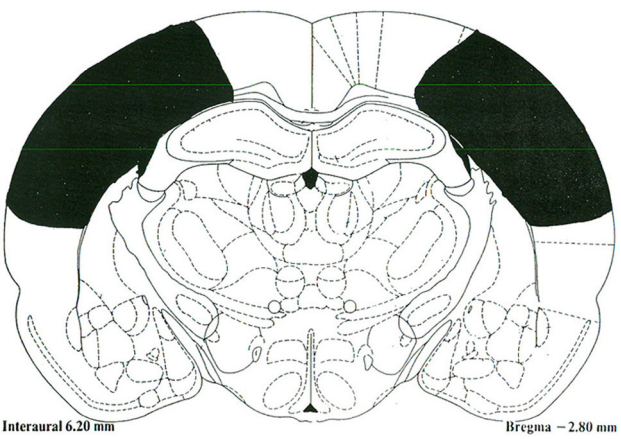

FIGURE 1 | A schematic representative lesion of the posterior parietal cortex projected unto a stereotaxic map of the rat brain [Paxinos and Watson (1997)]. *The Rat Brain: In Stereotaxic Coordinates.* San Diego, CA: Academic Press.

DATA ANALYSIS

For all three analyses a repeated measures ANOVA with groups (control and PC) as the between variable and trials (blocks 1, 2, and 3) as well as features (one and two) as the within variables was used. When applicable a Neman–Keuls paired comparison test was used. Even though rats could make multiple errors, the acquisition data were analyzed based only on whether the first response was an error or was correct and was displayed as mean percent correct. In contrast, for the size and color search analysis all errors were counted and were displayed as mean total for color or size errors.

ACQUISITION OF THE SEARCH TASK

The results are shown in **Figure 2** and indicate that for the control rats the mean percent correct performance improved across blocks of trials for both the one- and two-feature condition, but for the PC lesioned rats there was better performance for the one compared to the two-feature condition, but little improvement across blocks of trials. The analysis revealed a significant group effect [$F_{(1,\ 10)} = 8.26$, $p = 0.016$], a significant blocks of trials effect [$F_{(2,\ 20)} = 5.67$, $p = 0.011$], and a significant feature effect [$F_{(1,\ 10)} = 16.53$, $p = 0.002$], but no significant interactions. These data suggest that PC rats make many errors resulting in impaired performance especially for both the one- and two-feature condition suggesting that they are susceptible to discrimination problems as well as the making of illusory conjunction errors.

To analyze further whether the errors were either based on problems with size or color discrimination, the data were analyzed in terms of mean total number of color or size errors across blocks of trials for the one- and two-feature conditions. The results for mean number of errors for color are shown in **Figure 3** and indicate that for the control rats the mean total number of errors decreased across blocks of trials for both the one- and two-feature condition. For the first block the PC lesioned rats displayed a high mean total number of errors for the two-feature condition relative to the one-feature condition and for the one- and two-feature conditions for the control group. For the third block of trials the PC lesioned rats displayed a high mean total number of errors in both the one- and two-feature conditions relative to the control one- and two-feature conditions. The analysis revealed a significant group effect [$F_{(1,\ 10)} = 25.4$, $p < 0.0005$], a significant blocks of trials effect [$F_{(2,\ 20)} = 10.14$, $p = 0.0009$], a significant feature effect [$F_{(1,\ 10)} = 5.1$, $p = 0.047$], and a significant interaction between groups, blocks of trials, and features [$F_{(2,\ 20)} = 4.3$, $p = 0.028$]. A subsequent Newman–Keuls test for the interaction effect revealed that for the first block the PC lesioned rats displayed a significantly higher mean total number of errors for the two-feature condition relative to the one-feature condition and for the one- and two-feature conditions for the control group ($p < 0.01$). For the third block of trials the PC lesioned rats displayed a significantly higher mean total number of errors in both the one- and two-feature conditions relative to the control one- and two-feature conditions ($p < 0.05$). The results for color errors indicate that PC lesioned rats relative to controls made only a few errors in detecting the one feature component of the task, but they made many errors throughout all three blocks of trials for the two-feature condition suggesting the appearance of illusory conjunction errors.

The results for mean number of errors for size are shown in **Figure 4** and indicate that there are no obvious differences between the PC and control groups for either one or two features in part due to the variability in the results. A similar repeated measures ANOVA that was used to analyze search errors for color was used for search errors for size. The analysis revealed that there were no significant differences. Even though there was an increase in illusory conjunctions errors for both the PC lesion and control animals for size, this increase was not significant which is likely due to enhanced variability in performing the size discrimination.

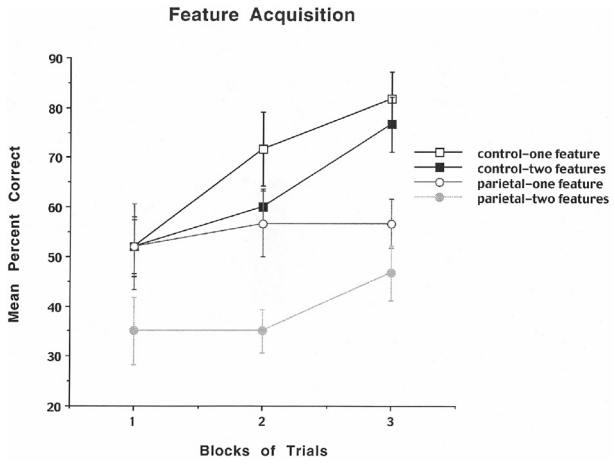

FIGURE 2 | Mean number of search errors for one or two features for control and parietal cortex lesioned rats as a function of blocks of trials. Each block consisted of 20 trials.

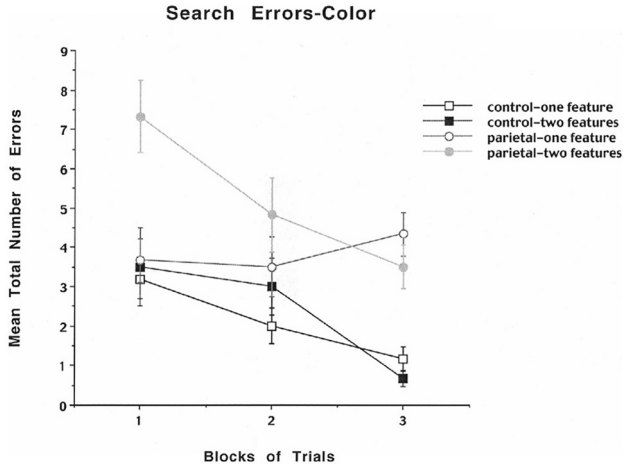

FIGURE 3 | Mean number of search errors for one or two features for object color for control and parietal cortex lesioned rats as a function of blocks of trials. Each block consisted of 20 trials.

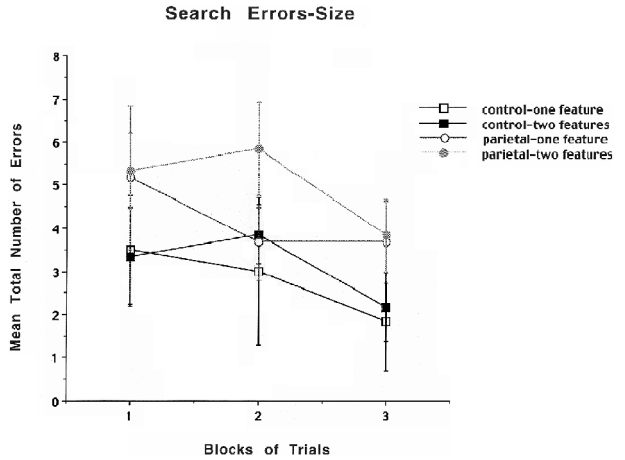

FIGURE 4 | Mean number of search errors for one or two features for object size for control and parietal cortex lesioned rats as a function of blocks of trials. Each block consisted of 20 trials.

DISCUSSION

The data show that the control animals displayed a small but not significant increase in errors for the two compared to the one-feature condition. It is assumed by Treisman's (1998) feature integration theory that the two-feature condition is more difficult than the one-feature condition requiring the recruitment of attentional processes, so there might be a possibility that the task for control rats was not difficult enough and thus requiring minimal recruitment of attentional processes. Even though the control rats did not differ significantly in terms of the one- vs. two-feature condition for shapes or color, there are also data with humans showing that using shapes and color that parallel the findings with rats in that there was no significant difference in latency to respond to the one compared to the two-feature condition (Shafritz et al., 2002). The data also show that PC lesions in rats appear to disrupt acquisition of the task, which could be due to the difficulty in discriminating the features of the task, but in the first two blocks of trials, the PC lesioned rats do not show a deficit for the one-feature condition, but show a clear deficit for the two-feature condition suggesting that the PC may indeed be involved in feature binding as reflected by illusory conjunction errors. The data with PC lesions in rats parallel the findings with PC in humans in that a bilateral parietal damaged patient made consistent illusory conjunction errors in a visual search task based on the conjunction of two features of an object (Robertson et al., 1997).

The results also show a significant increase in illusory conjunction errors for the PC lesioned rats relative to controls for color and relative to color discrimination, suggesting that the PC may support feature binding as it relates to color. The lack of a significant effect for size is likely due to the size difference of 2 cm that was used in this experiment, especially because in more recent research findings, it can be shown that rats in an exploratory-based paradigm detect a novelty change in size only when the size differs in 6 or 8 cm, but not 2 or 4 cm (unpublished observations). Even though the control rats appeared to have more difficulty with shapes compared to color, the previously mentioned study (Shafritz et al., 2002) reported that the participants were also less accurate with shapes compared to color, which is consistent with the rat data. Thus, it appears that the PC in rats supports the binding of visual features within objects or landmarks, a process which has been assumed to be mediated by spatial attention. One should also note that there is the possibility that the PC rats are performing a single feature match in the two-feature condition.

One additional role for the rodent PC could be to bind across modalities to maintain the association between landmark and spatial location information. In other words, the PC may not be involved in memory for a single landmark or a single spatial location, but rather in the processing that assigns a specific landmark to a specific spatial location. To test this hypothesis, rats with small lesions of the PC were tested in an object/spatial location paired-associate task that required concurrent memory for both object and spatial location information. In addition, memory for a landmark only or a spatial location only information was also assessed. The results indicated that small lesions of the PC as defined by Reep et al. (1994) and larger PC lesions disrupted learning of the object-place paired-associate task, but did not disrupt the learning of a spatial or object discrimination (Long et al., 1998). The deficit in the paired associate task (which requires memory for both landmark and spatial location information), in the absence of deficits in either the landmark or the spatial location only memory, supports the idea that the PC is involved in the memory for the binding of landmark and spatial location information. Even though there are many studies in humans that report on the role of PC in processing of objects or spatial locations, there are not many articles that have dealt with the binding of objects and locations. One study (van Asselen et al., 2009) examined a population of stroke patients with varying degrees of PC damage. The results showed that in a combined object-place task, there was an impairment that was primarily due to damage in the left posterior PC. Thus, there appear to be some parallels in the binding function between locations and landmarks in rats and humans.

Another role for the rodent PC could be to bind egocentric and allocentric information in long-term memory comes from a study by Rogers and Kesner (2007). They trained rats in two versions of a modified Hebb–Williams maze to test the role of the PC in processing egocentric and allocentric information during acquisition and retention. In the first version, unlike traditional Hebb–Williams mazes, the maze was made of 1.3 cm Plexiglas, measuring 25 cm in height with a 7.5 cm strip, also painted black, placed on the bottom of the barriers. This spatial arrangement allowed the rat to use extra maze cues. Extra maze cues included two posters, a map, and a hanging doll. Given that this maze allowed for the use of extra maze cues, learning might be primarily based on allocentric cues, so they labeled this task an allocentric task. The second maze used in these experiments was the same modified Hebb–Williams maze mentioned above; however, the walls were 50.8 cm high, made of 0.6 cm red Plexiglas. The apparatus was kept in a well-lit room with no windows or extramaze cues. This maze is assumed to be learned primarily on the basis of egocentric and local topological cues, because the walls were raised, made opaque, and there were few, if any,

extra maze cues. They labeled this task as an egocentric task. Bilateral lesions were made to PC before maze testing (acquisition) or after maze testing (retention). The results indicated that lesions of the PC impaired egocentric maze acquisition, but the animals had no difficulty in learning the allocentric version of the maze task. Similar deficits following PC lesions were reported by Boyd and Thomas (1977) during acquisition of the standard Hebb–Williams maze, which did not give the rats an opportunity to use extra maze cues. During retention, lesions of the PC produced a significant impairment on both maze versions, suggesting that the PC may be combining both egocentric and allocentric information during normal learning of the maze, but after a PC lesion the combined information may not be available to the animal. These results suggest that long-term retention of spatial information requires that the PC binds egocentric and allocentric information.

Thus, it appears that the PC in rats may play an important role in binding features of objects, cross-modal (objects and spatial locations), as well as egocentric and allocentric spatial processing.

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Damage to posterior parietal cortex impairs two forms of relational learning

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The posterior parietal cortex (PPC) is a component of a major cortico-hippocampal circuit that is involved in relational learning, yet the specific contribution of PPC to hippocampal-dependent learning is unresolved. To address this, two experiments were carried out to test the effects of PPC damage on tasks that involve forming associations between multiple sensory stimuli. In Experiment 1, sham or electrolytic lesions of the PPC were made before rats were tested on a three-phase sensory preconditioning task. During the first phase, half of the training trials consisted of pairings of an auditory stimulus followed by a light. During the other trials, a second auditory stimulus was presented alone. In the next phase of training, the same light was paired with food, but no auditory stimuli were presented. During the final phase of the procedure both auditory stimuli were presented in the absence of reinforcement during a single test session. As is typically observed during the test session, control rats exhibited greater conditioned responding to the auditory cue that was previously paired with light compared to the unpaired cue. In contrast, PPC-lesioned rats responded equally to both auditory cues. In Experiment 2, PPC-lesioned and control rats were trained in a compound feature negative discrimination task consisting of reinforced presentations of a tone-alone and non-reinforced simultaneous presentations of a light-tone compound stimulus. Control rats but not rats with damage to the PPC successfully learned the discrimination. Collectively, these results support the idea that the PPC contributes to relational learning involving multimodal sensory stimuli, perhaps by regulating the attentional processing of conditioned stimuli.

Keywords: medial temporal lobe, attention, associative learning, conditioned inhibition, parietal cortex

INTRODUCTION

The posterior parietal cortex (PPC), along with the retrosplenial cortex (RSP), provides the primary source of polymodal visuo-spatial information to the postrhinal cortex (POR), which in turn has reciprocal connections with entorhinal cortex and discrete regions of the hippocampus (Burwell and Amaral, 1998a,b; Burwell, 2000; Furtak et al., 2007). Thus, PPC is ideally situated to contribute significantly to hippocampal-dependent functions, such as relational or configural learning, which involve processing information about multiple stimuli (Rudy and Sutherland, 1989, 1995; Eichenbaum and Cohen, 2001; Ryan et al., 2010). Indeed, disconnecting the PPC from hippocampus has been shown to impair performance during an object-place paired associates task (Rogers and Kesner, 2007). However, few studies have examined the contribution of PPC to other, non-spatial forms of relational learning.

The present study used a sensory preconditioning task and a compound feature negative discrimination task to examine the role of the PPC in non-spatial relational learning involving multimodal sensory stimuli. These tasks were chosen for several reasons. First, previous studies from our laboratory demonstrated that damage to RSP impairs performance on both tasks (Keene and Bucci, 2008b; Robinson et al., 2011), thus, given the similar anatomical connections of PPC and RSP, we were interested in comparing the effects of PPC and RSP lesions in these forms of learning. Moreover, the effects of hippocampal damage or lesions of areas of rhinal cortex have also been tested in these paradigms (Nicholson and Freeman, 2000; Ward-Robinson et al., 2001; Talk et al., 2002; Campolattaro and Freeman, 2006a,b). A second reason was that these paradigms involve learning about relationships between *phasic* stimuli, which is a particularly important feature because it has previously been shown that PPC damage does not impair contextual fear conditioning (Keene and Bucci, 2008a), which requires the formation of associations between multiple *static* environmental stimuli.

The sensory preconditioning task (Experiment 1), adapted from Brogden (1939) was conducted in three phases. During the "preconditioning" phase, an auditory stimulus (e.g., a tone) was presented and followed immediately by a light on half of the trials. During the other half of the trials another auditory stimulus (e.g., white noise) was presented alone. No reinforcement was delivered during this phase. During the subsequent "conditioning" phase, the same light was presented and followed by food reward. Finally, during the "post-conditioning" phase, a single test session assessed conditioned responding (food cup behavior) in response to each of the auditory stimuli by presenting them alone. If rats formed an association between the auditory stimulus that was paired with light during preconditioning, and if the significance

of this relationship was updated after light → food conditioning, then food cup behavior was predicted to be particularly high in response to the paired stimulus, reflecting relational learning (Holland and Ross, 1983; Leising et al., 2007; Blaisdell et al., 2009; Robinson et al., 2011).

In Experiment 2, another set of PPC-lesioned rats was trained in a compound feature negative discrimination paradigm. Rats received two types of training trials: during reinforced trials, a tone was presented for 10 s and immediately followed by food reward; on non-reinforced trials, a light was presented concurrently with the tone and no food was delivered. Normal rats typically learn to approach the food cup in anticipation of receiving the food reward on tone-alone trials but withhold responding during light-tone simultaneous compound trials, indicating that rats form a relationship between the light and tone to inhibit responding (Chan et al., 2003).

MATERIALS AND METHODS

SUBJECTS

Male Long Evans rats weighing ∼225 g were obtained from Harlan Laboratories (Indianapolis, IN). Rats were housed individually and allowed seven days to acclimate to the vivarium with food available *ad libitum* (Purina standard rat chow; Nestle Purina, St. Louis, MO). Subsequently, rats were handled for 2 min per day for three days and weighed daily to establish baseline body weights, which were then gradually reduced to 85% of baseline over a seven-day period. Throughout the study, rats were maintained on a 14:10 light-dark cycle and monitored and cared for in compliance with the Association for Assessment and Accreditation of Laboratory Animal Care guidelines and the Dartmouth College Institutional Animal Care and Use Committee. All efforts were made to minimize discomfort for the animals.

SURGERY

Rats were anesthetized with isoflurane gas (1.5–3% in oxygen) and placed in a Kopf stereotaxic apparatus. To make bilateral electrolytic lesions of the PPC (Experiment 1, $n = 11$; Experiment 2, $n = 8$), the skin was retracted and small holes were drilled through the skull at the following eight locations (in mm): AP, −3.7, −4.7; ML, ±2.5, ±3.7; DV (from skull), −1.6, −1.8. These coordinates were based on previous reports that targeted the PPC (Bucci and Chess, 2005; Keene and Bucci, 2008a; Kesner, 2009) with boundaries based on thalamic and cortical connections (Chandler et al., 1992; Reep et al., 1994; Bucci et al., 1999; Paxinos and Watson, 2007). An electrode that was epoxy-coated except for the tip was lowered into each coordinate and a 2.5-mA current was passed through the tip for 15 s per lesion site. The needle was slowly retracted after the current was delivered and the skin was stapled together with wound clips. Electrolytic lesions were used to provide control over the extent of damage, which was an important factor in this study given the close proximity of RSP, which also provides visuo-spatial input to the medial temporal lobe (Burwell and Amaral, 1998a; van Groen and Wyss, 1990, 1992, 2003) and because we wanted to directly compare the effects of PPC-lesions to RSP lesions that were carried out using electrolytic methods in prior studies (Keene and Bucci, 2008a,b). Control rats (Experiment 1, $n = 15$; Experiment 2, $n = 8$) received sham lesions consisting of a craniotomy and shallow, non-puncturing burr holes to minimize damage to underlying cortex. Rats were allowed to recover for two weeks before behavioral training.

BEHAVIORAL APPARATUS

Conditioning chambers

The behavioral apparatus was obtained from Med Associates Inc. (St. Albans, VT) and consisted of standard operant conditioning chambers (24 × 30.5 × 29 cm) connected to a computer and enclosed in sound-attenuating chambers (62 × 56 × 56 cm) outfitted with an exhaust fan to provide airflow and background noise (∼68 dB). The operant chambers consisted of aluminum front and back walls, clear acrylic sides and top, and grid floors. A dimly illuminated food cup was recessed in the center of the front wall. A 2.8-W house light was mounted on the opposite wall and served as the visual stimulus. During stimulus presentation, the light flashed at a frequency of 2 Hz during preconditioning and conditioning. A speaker was located 15 cm above and to the right of the food cup and was used to present the tone (1500 Hz, 78 dB) and white noise (78 dB, Experiment 1 only) stimuli. A red, 2.8-W bulb was mounted on the ceiling of the sound-attenuating chamber to provide background illumination. A pair of infrared photocells was mounted just inside the food cup to detect head entries into the cup. Surveillance cameras located inside the sound attenuating chambers were used to monitor the rats' behavior.

Open field apparatus

Locomotor activity was assessed in an open field apparatus (43.2 × 43.2 × 30.5 cm) composed of Plexiglas walls and floor (Med Associates, Inc.). The chambers were equipped with 16 infrared photobeams that were arrayed 5.5 cm apart. Photobeam interruptions were recorded by a computer running custom Open Field Activity Monitoring software (Med Associates Inc.) that calculated the total distance traveled.

BEHAVIORAL PROCEDURES

Experiment 1

Sensory preconditioning. A schematic diagram of the sensory preconditioning task is shown in **Figure 1A**. During the preconditioning phase, rats received four daily 64-min training sessions each consisting of 12 trials. On six of the trials, one of the auditory stimuli (the paired stimulus) was presented for 10 s and followed immediately by the 5-s flashing light stimulus. During the other six trials the other auditory stimulus (the unpaired stimulus) was presented alone for 10 s. The trials types were randomly intermixed with an average inter-trial interval (ITI) of 4.5 min and the use of the tone and white noise as the paired and unpaired auditory stimuli was counterbalanced across groups. During the conditioning phase, rat received seven daily 64-min conditioning sessions each of which consisted of eight presentations of the flashing light (5 s in duration, average ITI of 8 min) followed immediately by delivery of two 45-mg food pellets (Noyes, New Brunswick, NJ). Note that neither auditory stimulus was presented during the conditioning phase. Finally, the

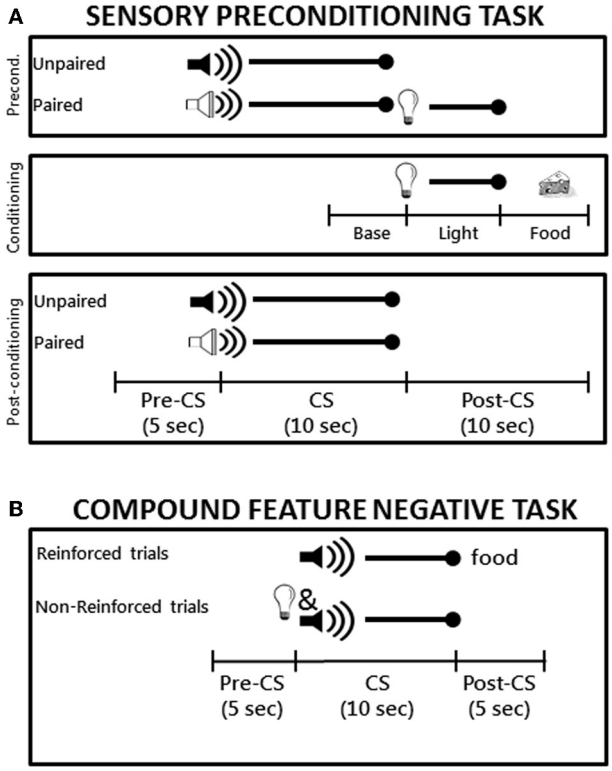

FIGURE 1 | (A) Schematic diagram the sensory preconditioning task used in Experiment 1. The time line and epochs (Preconditioning: Baseline, Light, Food; Post-conditioning: Pre-CS, CS, Post-CS) noted on the bottom refer to the time periods used in the analyses described in the Materials and Methods. **(B)** Schematic diagram of the compound feature negative discrimination task used in Experiment 2. Rats were tested on a total of 8 daily conditioning sessions.

post-conditioning phase consisted of a single test session during which each of the two auditory stimuli were presented alone (six times each) in separate intermixed trials (78-min session).

Locomotor activity. After the completion of the post-conditioning phase, rats were placed individually in a novel open field chamber for 10 min to test for potential activity changes induced by PPC-lesions.

Experiment 2

A schematic diagram of the compound feature negative discrimination task is shown in **Figure 1B**. Rats were magazine trained during a single 64 min session during which two 45-mg food pellets were randomly delivered 16 times. Training took place over eight daily sessions that lasted 64 min each and included 16 trials of two types. Rats received four trials per session consisting of a 10-s presentation of the tone followed immediately by delivery of two 45-g food pellets. For the other 12 trials, the panel light was presented simultaneously with the tone (10 s) and no food was delivered on these trials. The two trial types occurred randomly during the session and the order of trials differed on each day. The variable ITI averaged 4 min during magazine training and conditioning sessions.

BEHAVIORAL OBSERVATIONS AND DATA ANALYSIS

Experiment 1

Sensory preconditioning. Breaks in the photobeam located across the entry of the food cup were monitored by the computer. The amount of time the beam was broken served as the measure of conditioned food cup behavior. During conditioning, beam break data was collected during the 5-s period prior to onset of the visual stimulus ("Baseline" epoch), during the 5-s presentation of the visual stimulus ("Light" epoch) and during the 5 s period in which food was delivered ("Food" epoch) as shown in the schematic in **Figure 1A**. Data from the Light and Food epochs were subjected to repeated measures analysis of variance (rmANOVA) with Group (control, PPC-lesion) as the between-subjects variable and Session (1–7) as the within-subjects variable.

During the post-conditioning test session, beam break data was collected during three epochs: the 5-s period prior to onset of the auditory conditioned stimuli ("Pre-CS" epoch), the 10-s period during presentation of the auditory stimuli ("CS" epoch), and during the 10-s period following presentation of the auditory stimuli ("Post-CS" epoch). Data from the CS and Post-CS epochs were subjected to rmANOVA with Group (control, PPC-lesion) as the between-subjects variable and Trial Type (Paired stimulus, Unpaired stimulus) as the within-subjects variable. Significant main effects were followed up with appropriate pair-wise comparisons (two-tailed *t*-tests). Data from the Post-CS epoch were particularly important to analyze because this period corresponded to the time that the light was presented after the auditory stimulus in the preconditioning phase and also to the time that food would have been presented during light → food conditioning in the conditioning phase. An additional comparison of the strength of sensory preconditioning between the control and lesioned groups was carried out on the Post-conditioning session data by calculating a difference score, defined as the amount of responding observed during the Post-CS period following presentation of the paired auditory stimulus divided by the sum of the Post-CS responding observed following each of the auditory stimuli. Using one-sample *t*-tests, the resulting values for each group were compared to an expected value of 50% (i.e., chance), which would indicate no sensory preconditioning.

Locomotor activity. Open field activity data was analyzed with rmANOVA with Group (control, PPC-lesion) as the between-subjects variable and Epoch (1-min periods) as the within-subjects variable. An alpha level of 0.05 was used in all analyses.

Experiment 2

Compound feature negative discrimination task. As in Experiment 1, breaks in the photobeam located across the entry of the food cup were monitored by the computer and the amount of time the beam was broken served as the measure of conditioned food cup behavior. As demonstrated in previous studies (Holland et al., 1999; Keene and Bucci, 2008b), rats typically exhibit increasing levels of responding on both trial types for the first few sessions and do not discriminate between them. Indeed, the main data of interest are the levels of conditioned responding that are achieved when rats have reached stable performance

levels on both types of trials. Thus, the data from the last two sessions were averaged and subjected to rmANOVA with Group (control, PPC-lesion) as the between-subjects variable and Trial Type (reinforced, non-reinforced) as the within-subjects variable. Analyses were conducted during the 5-s period prior to CS onset (Pre-CS responding), during presentation of the CS, and during the 5 s after the CS was turned off (Post-CS responding). Significant main effects were followed up with appropriate pair-wise comparisons (two-tailed *t*-tests). In addition, a difference score was calculated by subtracting responding during non-reinforced trials from responding during reinforced trials during the last two sessions. This was used to assess the magnitude of the discrimination in each group. An alpha level of 0.05 was used in all analyses.

LESION VERIFICATION AND ANALYSIS

After the behavioral procedures were completed, rats were deeply anesthetized with an overdose of pentobarbital sodium and phenytoin sodium (Euthasol, Virbac Animal Health, Fort Worth, TX) and transcardially perfused with 0.9% saline for 5 min, followed by 10% buffered formalin. Brains were sectioned on a freezing microtome (60 μm) and Nissl-stained using thionin. For each animal, coronal sections at four AP locations (from Bregma: −3.36, −3.72, −4.20, −4.80; see **Figure 2B**) along the rostrocaudal extent of the PPC were used to assess the amount of tissue damage. Using StereoInvestigator software (Version 9; Microbrightfield, Inc., Williston, VT) and a compound microscope (Axioskop I, Zeiss, Inc.), gross tissue damage as necrosis, missing tissue, or marked thinning of the cortex was identified. For each coronal section, areal measurements were obtained using the StereoInvestigator Cavalieri estimator probe with 50 μm grid spacing. Lesion size is expressed as the percentage of damage to the target region divided by the total area of the target region.

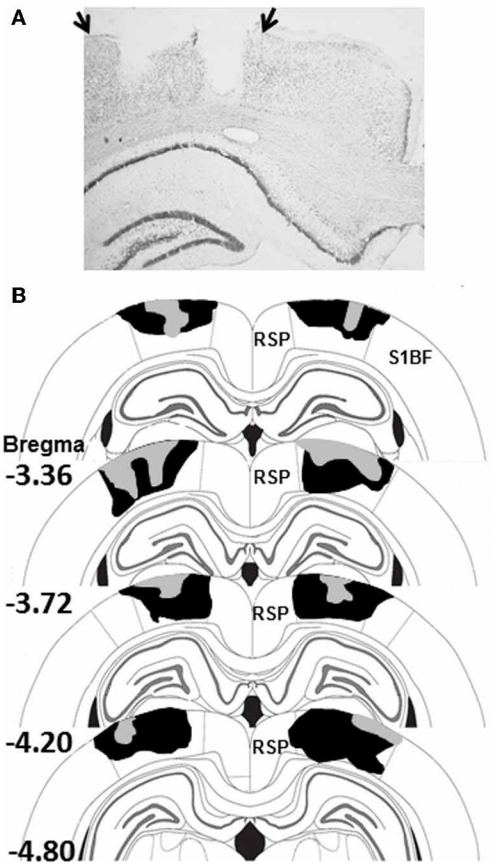

FIGURE 2 | (A) Photomicrograph of a PPC-lesion illustrating typical damage to PPC on one side of the brain. The arrows indicate the boundaries of PPC. **(B)** Schematic diagram indicating the largest (black) and smallest (gray) lesions of PPC in Experiment 1 (adapted from Paxinos and Watson, 2007). Abbreviations: RSP, restrosplenial cortex; S1BF, somatosensory cortex barrel fields.

RESULTS

HISTOLOGY

Electrolytic damage to the PPC is displayed in the photomicrograph in **Figure 2A** and the largest and smallest of the 11 PPC-lesions from Experiment 1 are shown in **Figure 2B**. Bilateral PPC damage was observed in all rats and the average area of PPC damaged on each section analyzed in Experiment 1 was 49 ± 3% (range 36–69%). Minor unilateral damage to the RSP was observed in one animal and minor unilateral damage to somatosensory cortex was observed in two animals. Minor unilateral damage to the corpus callosum was observed in 4 animals. In Experiment 2, damage to the PPC in lesioned rats was similar to that observed in Experiment 1 and to previous studies from our lab (Keene and Bucci, 2008a). Bilateral PPC damage was observed in all rats and the average area of PPC damaged on each section analyzed was 48 ± 3% (range 33–60%).

BEHAVIOR

Experiment 1

Sensory preconditioning. As shown in **Figure 3A** (left panel), as training progressed during the conditioning phase, rats in both groups exhibited increased food cup behavior during presentation of the light (Light epoch). This was confirmed by a rmANOVA that revealed a significant main effect of Session [$F_{(6, 144)} = 55.0$, $p < 0.001$]. The main effect of Group and the Group X Session interaction were not statistically significant ($ps > 0.2$), indicating that control and PPC-lesioned rats comparably learned the association between the light and food. Similarly, analysis of data from the Food epoch (**Figure 3A**, right panel) revealed that both groups increased food cup responding across training sessions [$F_{(6, 144)} = 90.5$, $p < 0.001$]. The main effect of Group and the Group X Session interaction were not statistically significant ($ps > 0.2$), suggesting that control and PPC-lesioned rats were comparably motivated to retrieve food.

The critical test session data collected during post-conditioning phase is illustrated in **Figure 3B**. A rmANOVA that compared the food cup behavior of control and PPC-lesioned rats during the Post-CS epoch revealed a significant main effect of Trial Type [$F_{(1, 24)} = 11.25$, $p < 0.01$] and a significant Trial Type X Group interaction [$F_{(1, 24)} = 4.68$, $p < 0.05$]. Importantly, there was no main effect of Group ($p > 0.1$) indicating that control and PPC-lesioned rats exhibited similar overall levels of food cup responding. Subsequent paired *t*-tests on test session

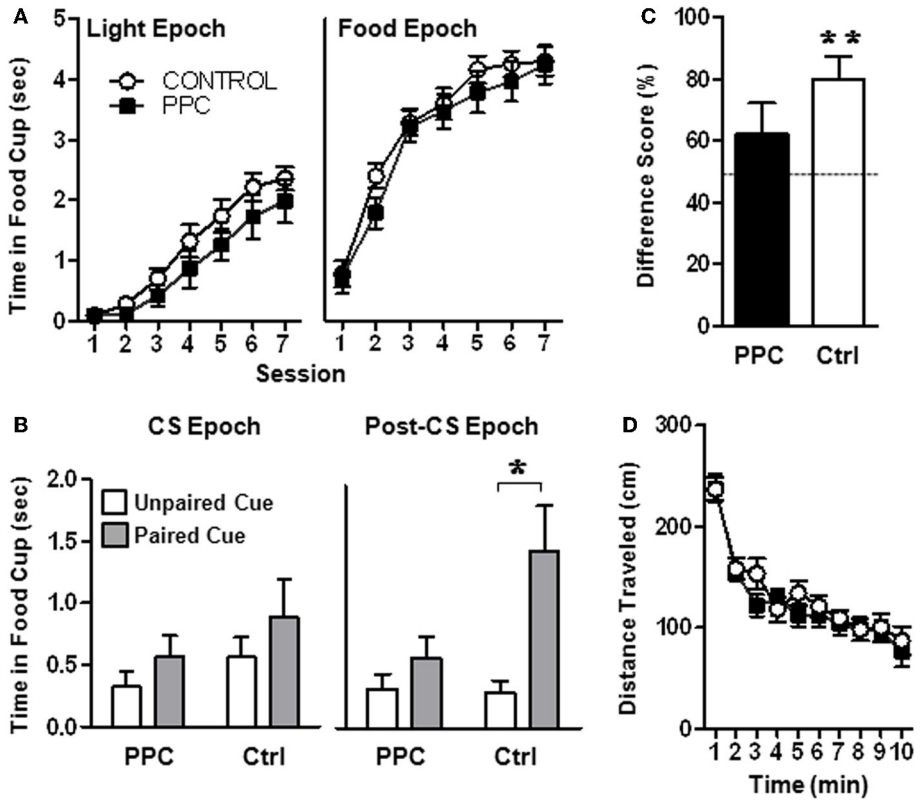

FIGURE 3 | Experiment 1. PPC-lesioned rats exhibit impaired sensory preconditioning. **(A)** Food cup responding during the Light epoch (left panel) and during the Food epoch (right panel) during Phase 2 of the sensory preconditioning task. No group differences were observed, indicating that PPC damage did not affect light-food conditioning or food retrieval. **(B)** Food cup responding during the CS epoch (left panel) and the Post-CS epoch (right panel) following presentation of the two auditory stimuli during the post-conditioning phase. Control but not PPC-lesioned rats exhibited sensory preconditioning, evidenced by greater food cup responding during presentation of the auditory stimulus that was previously paired with the light compared to the unpaired auditory stimulus during the Post-CS epoch. **(C)** Food cup behavior difference scores calculated from the Post-CS epoch during the test session. Control, but not PPC-lesioned rats exhibited difference scores significantly different from 50%, indicating that during the Post-CS epoch, more time was spent with the snout in the food cup on paired stimulus trials compared to unpaired stimulus trials. **(D)** Open field activity demonstrating that the distance traveled by PPC-lesioned rats ($n = 11$) did not differ from that of control rats ($n = 15$) and that both groups similarly habituated to the open-field over time. Data are mean ± standard error. *Indicates a significant ($p < 0.05$) difference in food cup behavior by control rats on unpaired vs paired (sensory preconditioned) trials. **Indicates a significant ($p < 0.05$) difference from chance (50%).

data from the Post-CS epoch (**Figure 3B**, right panel) revealed that control rats spent more time in the food cup on trials in which the paired auditory stimulus was presented compared to trials in which the unpaired auditory stimulus was presented [$t_{(14)} = -3.4$, $p < 0.01$], indicating that control rats formed a stimulus–stimulus association during the preconditioning phase that was updated following the light-food conditioning phase. Unlike control rats, animals with PPC damage exhibited similar food cup responding during the Post-CS epoch regardless of whether the paired or unpaired auditory stimulus was presented. The rmANOVA conducted on the CS-epoch data did not reach statistical significance (**Figure 3B**, left panel; $ps > 0.1$).

A complementary analysis was conducted using difference scores (calculated by dividing the time spent in the food cup during the Post-CS epoch following presentation of the paired stimulus by the sum of the Post-CS responding observed following presentation of each auditory stimulus during the critical post-conditioning-test session), as presented in **Figure 3C**. Control rats had a mean difference score that was significantly higher than 50% [$t_{(14)} = 4.1$, $p < 0.001$; mean = 80.1 ± 7.2%] but PPC-lesioned rats did not ($p > 0.2$; mean = 61.9 ± 10.3%). These data are consistent with the results of the primary rmANOVA above in suggesting that PPC damage impaired sensory preconditioning.

Locomotor activity. Assessment of open field activity (**Figure 3D**) revealed that there were no differences in total activity or habituation to the open field ($ps > 0.6$) between control and PPC-lesioned rats.

Experiment 2

Figure 4A illustrates conditioned responding during presentations of the tone and light-tone compound stimuli across all eight sessions of the compound feature negative discrimination task. **Figure 4B** displays average conditioned responding during the last two sessions, when stable performance is typically observed. A rmANOVA on the data from the last two sessions revealed a significant main effect of Trial Type

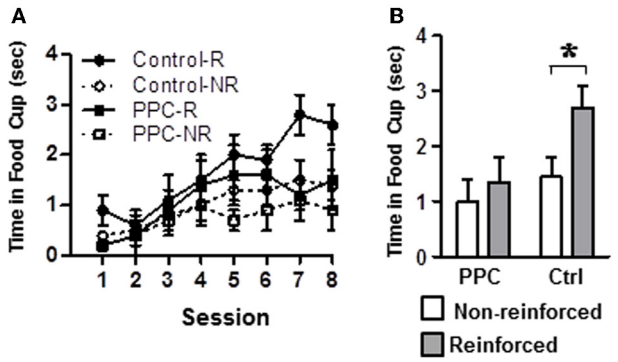

FIGURE 4 | Experiment 2. Damage to PPC impaired learning on the compound feature-negative discrimination task. **(A)** Conditioned food cup behavior following presentations of the tone-alone (reinforced) and following presentations of the compound stimulus (light-tone, non-reinforced) across all eight conditioning sessions. **(B)** Combined data from conditioning sessions 7 and 8 during which stable performance is typically observed. Data are mean ± standard error. Abbreviations: R, reinforced stimulus; NR, non-reinforced stimuli. *Indicates a significant ($p < 0.05$) difference in food cup behavior by control rats on R verses NR trials.

$[F_{(1, 14)} = 24.1, p < 0.001]$ and a significant Trial Type X Group interaction $[F_{(1, 14)} = 7.7, p < 0.02]$, but no significant effect of Group, indicating that the groups differed in their ability to discriminate between the two trials, but not in their overall responding. Subsequent analysis revealed that control rats exhibited significantly more food cup behavior during reinforced trials compared to non-reinforced trials $[t_{(7)} = 5.4, p < 0.001]$. In contrast, PPC-lesioned rats exhibited comparable levels of responding on both trial types $[t_{(7)} = 1.5, p > 0.2]$. Additional comparisons indicated that on reinforced trials control rats spent more time in the food cup than did PPC-lesioned rats $[t_{(14)} = 2.4, p < 0.03]$. There was no significant group difference in responding during the non-reinforced trials $[t_{(14)} = 0.9, p > 0.4]$. The magnitude of the discrimination, as assessed by the difference in responding on reinforced and non-reinforced trials, also differed significantly between control and PPC-lesioned rats $[t_{(14)} = 2.8, p < 0.02]$. The difference scores for control and PPC-lesioned rats were 1.3 ± 0.2 s and 0.3 ± 0.2 s, respectively, indicating that PPC-lesions impaired the ability to discriminate between the two trials types, consistent with the findings of the primary ANOVA above.

Group differences in food cup behavior exhibited during the 5-s period prior to CS onset (i.e., pre-CS responding) were analyzed to test for differences in baseline responding. The amount of food cup behavior exhibited prior to the start of a trial was very low and did not differ between control and PPC-lesioned rats $[F_{(1, 14)} = 0.02, p > 0.9]$. The mean amount of time spent with the snout in the food cup during the pre-CS period was 0.4 ± 0.1 s for both groups. Responding during the 5-s period immediately after the tone was turned off and food was delivered (i.e., Post-CS responding) was also examined to assay for potential group differences in retrieving food. A rmANOVA indicated that Post-CS responding was comparable between control and PPC-lesioned rats $[F_{(1, 14)} = 2.7, p > 0.1]$. The mean time spent in the food cup during the Post-CS epoch was 4.3 ± 0.2 s and 3.9 ± 0.2 s for control and PPC-lesioned rats, respectively.

DISCUSSION

The present study tested the effects of PPC damage on two non-spatial tasks that involve encoding information about multiple phasic sensory stimuli. In Experiment 1, sensory preconditioning occurred in control but not PPC-lesioned rats. In Experiment 2, PPC damage impaired the ability of rats to learn a conditional discrimination between a reinforced single stimulus (e.g., a tone) and a non-reinforced compound stimulus (e.g., tone and light).

One objective of the present study was to compare the effects of damage to the PPC with previous observations following damage to the RSP. Of particular relevance, a recent series of studies demonstrated that RSP-lesioned rats were impaired in their ability to solve a variety of tasks that involved the formation of stimulus–stimulus associations regardless of whether stimuli are presented simultaneously (Keene and Bucci, 2008b), serially, or in the absence of reinforcement (Robinson et al., 2011). In addition, RSP damage also impairs contextual fear conditioning, which requires the formation of associations between multiple *static* environmental cues (Keene and Bucci, 2008a). These findings are consistent with those of Gabriel and colleagues who demonstrated that neurons in the posterior cingulate cortex of rabbits (thought to be comparable to RSP in rats) are sensitive to the formation of associations between a tone and different contexts in an approach/avoidance discrimination task (Freeman et al., 1996; Smith et al., 2004). Collectively, these data support the notion that RSP has a general role in forming stimulus–stimulus associations, regardless of whether the cues are static or phasic. Therefore, RSP may be essential for binding cues together to facilitate learning about behaviorally relevant stimuli.

Thus, one interpretation of the present results is that PPC damage also produces a general impairment in the ability to form stimulus–stimulus associations. Importantly, however, a shortcoming of this interpretation is that unlike RSP damage, PPC damage does not impair contextual fear conditioning (Keene and Bucci, 2008a). Perhaps rather than having a general role in the formation of stimulus–stimulus associations, the PPC contributes to relational learning situations in which stimuli are phasic and therefore more likely to garner attention compared to static cues. This possibility is consistent with a substantial literature indicating that PPC neurons fire transiently during the onset of a stimulus, or in response to a change in a stimulus, but stop firing during sustained presentation of a stimulus (Mountcastle et al., 1975; Robinson and Goldberg, 1978; Bushnell et al., 1981). Similarly, the PPC has repeatedly been shown to mediate increases in attention that are necessary for processing changes in the meaning of individual stimuli or changes in the relationships between stimuli (Bucci et al., 1998; Fox et al., 2003; Bucci and Chess, 2005; Bucci and Macleod, 2007; Maddux et al., 2007; Bucci, 2009). With respect to the sensory preconditioning task used in the present study, contemporary learning theories (Pearce and Hall, 1980; Wilson et al., 1992) maintain that attentional processing would be high because the light is first non-reinforced during the preconditioning phase, but then followed by food reward during

the conditioning phase. Thus, if PPC mediates relational learning about phasic stimuli with ambiguous or changed meanings, then PPC-lesioned rats would be impaired in their ability to update the significance of the tone-light relationship and thus subsequently fail to discriminate between the two auditory stimuli during the post-conditioning test session.

A potential flaw in this explanation lies in the fact that the meaning of the light also changed (i.e., first non-reinforced, then later paired with food), which would lead to the prediction that PPC-lesioned rats would also be impaired in learning the light-food relationship. Indeed, this was true in similar study (Bucci and Chess, 2005), but not in the present study. However, a key difference may be that in the study by Bucci and Chess (2005), the light was always presented alone in the non-reinforced phase, rather than being preceded by a tone (present study). Indeed, it has been suggested that pairing the tone and light in the sensory preconditioning paradigm may "protect" the light from latent inhibition, leading to intact learning in the conditioning phase of the sensory preconditioning task (Pfautz et al., 1978).

A similar attentional account may also explain the deficits observed in the compound feature negative discrimination task in Experiment 2. In that paradigm, tone-alone trials were always reinforced, while light-tone trials were always non-reinforced. Although there was no change in the meaning of the stimuli as there was in Experiment 1, it is important to note that the procedure used in the compound feature negative discrimination task amounts to a partial reinforcement paradigm, in that the tone is only reinforced on a subset of trials. As described previously, partial reinforcement contingencies typically enhance attentional processing of conditioned stimuli (Pearce and Hall, 1980). The conceptualization that PPC is particularly involved in processing changes in stimuli as described above also may explain the absence of impairment in contextual fear conditioning (Keene and Bucci, 2008a). Indeed, one difference between the conditioning tasks used here and contextual fear conditioning is that the conditioned stimuli in the latter paradigm are static cues. In other words, the contextual stimuli in the fear conditioning task are always present, regardless of whether footshock is delivered. In contrast, the tasks used in the present study involved phasic cues, which are only presented for short periods of time. Future studies could investigate the contribution of PPC to attentional processing during relational learning by systematically manipulating attentional load in permutations of the tasks used here.

Evidence that PPC contributes to relational learning informs the question of how different cortico-hippocampal circuits contribute to medial temporal lobe dependent learning and memory. Hippocampal damage has been shown to impair performance in a serial feature negative discrimination task (Holland et al., 1999) but spares learning a compound feature negative discrimination (Solomon, 1977; Chan et al., 2003). In contrast, PPC-lesions impair compound feature negative discrimination (Experiment 2). In addition, hippocampal damage has been shown to have an equivocal effect on sensory preconditioning, with some studies reporting deficits (Talk et al., 2002) and others observing no effects (Ward-Robinson et al., 2001). These findings support the notion that PPC may have a distinct role from the hippocampus during relational learning. This is consistent with recent theories delineating functional distinctions of a medial temporal lobe system believed to support episodic memory (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007). It is also noteworthy that damage to perirhinal cortex (PER) impairs sensory preconditioning (Nicholson and Freeman, 2000), compound feature negative discrimination (similar to Keene and Bucci, 2008b) and compound feature positive discrimination while having no effect on learning a serial feature positive discrimination (Campolattaro and Freeman, 2006a,b). Based on these findings, it was suggested that PER may play a role in resolving ambiguity in discriminations with overlapping stimulus elements (Campolattaro and Freeman, 2006a,b). Thus, it is possible that PER, PPC, and RSP contribute to complex learning paradigms by resolving stimulus ambiguity for overlapping stimulus elements, by allocating attention to changes in meaningful cues and by forming or mediating associations between multiple stimuli, respectively. These proposed functions of PER and RSP are consistent with another recent study that found unique contributions of CA1 and dorsocaudal medial entorhinal (dcMEC) cortex to the disambiguation of overlapping experiences (Lipton et al., 2007). Critical to the present discussion, this study establishes that nearby cortical structures (i.e., dcMEC) make important and distinct contributions to hippocampal function in resolving ambiguity for closely related or overlapping experiences. This idea, along with the present findings, provides an intriguing avenue for future research regarding the unique contributions of closely related brain areas such as PPC, PER, RSP, and the hippocampus.

The PPC is strongly connected with visuo-spatial areas (Miller and Vogt, 1984; Kolb and Walkey, 1987; Reep et al., 1994) and therefore, it is possible that the observed deficits in the present study could merely be due to an inability to process visual stimuli. Similarly, the use of electrolytic techniques may have damaged fibers of passage from these areas. This does not seem likely, however, since conditioning to the light was comparable in the control and PPC-lesioned groups during the sensory preconditioning task. It is also unlikely that alterations in motivation levels can explain the deficits in either task, since PPC-lesioned rats were no different from controls in approaching the food cup and consuming food when was delivered. Likewise, the impairments in conditioned responding during the test phase of the sensory preconditioning task or during the compound feature negative discrimination task were not due to lesion-induced changes in locomotor activity. Instead, the present findings support the notion that PPC contributes to hippocampal-dependent forms of relational learning, perhaps by regulating attentional processing of specific cues. In addition, these data are consistent with the notion that separate components of cortico-hippocampal circuits may have discernible roles in medial temporal lobe related behavior.

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Posterior parietal cortex dynamically ranks topographic signals via cholinergic influence

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The hypothesis to be discussed in this review is that posterior parietal cortex (PPC) is directly involved in selecting relevant stimuli and filtering irrelevant distractors. The PPC receives input from several sensory modalities and integrates them in part to direct the allocation of resources to optimize gains. In conjunction with prefrontal cortex, nucleus accumbens, and basal forebrain cholinergic nuclei, it comprises a network mediating sustained attentional performance. Numerous anatomical, neurophysiological, and lesion studies have substantiated the notion that the basic functions of the PPC are conserved from rodents to humans. One such function is the detection and selection of relevant stimuli necessary for making optimal choices or responses. The issues to be addressed here are how behaviorally relevant targets recruit oscillatory potentials and spiking activity of posterior parietal neurons compared to similar yet irrelevant stimuli. Further, the influence of cortical cholinergic input to PPC in learning and decision-making is also discussed. I propose that these neurophysiological correlates of attention are transmitted to frontal cortical areas contributing to the top-down selection of stimuli in a timely manner.

Keywords: sustained attention, acetylcholine, norepinephrine, prefrontal cortex, posterior parietal cortex, P300, contingent negative variation, muscarinic

INTRODUCTION: PARIETAL COMPONENT OF A NEURONAL CIRCUIT MEDIATING VIGILANCE

As part of the dorsal stream of visual processing, one of the hallmark functions the posterior parietal cortex (PPC) is the orientation of a subject to novel or meaningful stimuli. Critchley exhaustively documented that patients with unilateral damage to the PPC demonstrate neglect, a clinical syndrome characterized by an inability to report to stimuli presented on the contralateral side (Critchley, 1953). Posner and colleagues integrated data from single neuron recordings in monkeys, imaging studies and the study of patients with parietal lobe injuries to propose a theory that neglect results from an impaired ability to disengage attention from non-neglected side of space (Posner and Raichle, 1994). In rodents unilateral lesions in an anatomical homolog of the PPC produced persistent contralesional neglect to visual, auditory, and tactile stimuli, and disorders of spatial processing (King and Corwin, 1993; Reep and Corwin, 2009).

A series of neurophysiological studies in non-human primates provide evidence indicating that PPC neural activity represents the intentions of a subject to move in space, and that the PPC acts to guide effectors such as hands and eyes throughout space (Mountcastle et al., 1975; Kalaska, 1996; Snyder, 2000; Andersen and Buneo, 2002; Scherberger et al., 2005). Contrasting evidence indicates that PPC activity correlates with covert shifts in attention in the absence of effector movement (Colby and Goldberg, 1999; Bisley et al., 2004; Bisley and Goldberg, 2006; Ipata et al., 2006). An integration of the two neurophysiological models of parietal function complements the observations found in clinical research, namely that loss of parietal function impairs attention to and moving through contralateral space (Rushworth and Taylor, 2006). Taken together, the role of the PPC may then be to bias the detection and selection of sensory inputs from multiple modalities and to project target information to motor areas (Posner et al., 1980; Kastner and Ungerleider, 2000)[1].

This review proposes the hypothesis that the PPC ranks and highlights behaviorally relevant stimuli in order to aid detection and guide navigation. The neural circuitry influencing parietal processing is described, including the prefrontal cortex and the neuromodulatory influence of the basal forebrain cholinergic system (BFCS) to PPC, and this review makes the case that this circuitry is necessary for continually updating the ranking of topological stimuli, such as in the presence of task-irrelevant stimuli or rule changes requiring new learning. The possible contribution of ascending noradrenergic (NE) projections is also discussed. Although there is less direct evidence of the NE influence over parietal processing in attention, NE has an effect on evoked responses measured from sensory cortices. Further, recordings from ascending NE projections indicate that in conditions requiring global enhancement of arousal these inputs may facilitate processing of thalamocortical signals.

[1]I use the term "detection" to describe a cognitive process consisting of "…the entry of information concerning the presence of a signal into a system that allows the subject to report the existence of the signal by an arbitrary response indicated by the experimenter" (15).

THE POSTERIOR PARIETAL CORTEX IN RODENT MODELS OF ATTENTION

IDENTIFICATION OF THE ANATOMICAL HOMOLOG OF RODENT POSTERIOR PARIETAL CORTEX

Anatomically, the PPC of primates includes the superior and inferior parietal lobules. The superior lobules are comprised of Brodmann Areas (BA) 7 and 5, and the inferior lobules are comprised of BA 39 and 40. In monkeys and humans an intraparietal sulcus (IPS) delineates the superior and inferior lobules, and in monkeys neuronal activity within the lateral IPS corresponds to representations of salient stimuli in allocentric space (Colby and Goldberg, 1999), whereas activity in the medial IPS corresponds to the intention of a subject to reach for a target (Cohen and Andersen, 2002). The PPC expanded markedly in humans relative to monkeys, and evidence for homologous structures between the two is far from clear, though evidence for a human homolog of macaque LIP (Sereno et al., 2001), and motion sensitive activations were found in the ventral intraparietal sulcus (VIPS) and the VIP of macaques (Vanduffel et al., 2001, 2002).

In rats, the parcellation of PPC is not as precise. Anatomical features of the PPC include an interconnection to aspects of the visual system, including the frontal eye fields, pulvinar, ventrolateral thalamic nuclei (Leichnetz, 2001), and superior colliculus (Pare and Wurtz, 1997). In rats, the region considered to be a homolog to the primate PPC is generally defined as a region 3.5–5.0 mm caudal to the bregma and extending 1.5–5.0 mm lateral from the midline (Reep et al., 1994; Reep and Corwin, 2009). Rat PPC has reciprocal connections with the lateral dorsal and lateral posterior thalamic nuclei, similar to that of primates (Chandler et al., 1992). The PPC also has connections with medial agranular and orbital cortex, and is connected to auditory, somatosensory, and visual cortical areas (Reep et al., 1994). Further, basal forebrain cholinergic neurons project to the PPC of rats (Bucci et al., 1999). Although the distinctions of function (i.e., the parietal reach region vs. visual salience maps of the LIP) between subfields of the PPC have not been delineated in rodents, observations from the anatomical studies listed above support the general hypothesis that rat PPC is homologous to primate PPC, and is important for integrating multiple modes of sensory input for attentional processing.

PARIETAL CORTEX DYNAMICALLY RANKS RELEVANT SIGNALS IN VISUAL ATTENTION TASKS

There are two commonly used tasks to assess visual attention in rodents, the first being the 5 choice serial reaction task (5CSRTT) that was modeled after human continuous performance tasks (Carli et al., 1983; Bari et al., 2008), In the 5CSRTT, food-deprived rodents must monitor a horizontal array of five lights for brief, unpredictable flashes, and respond by nosepoking into the hole that flashed the light. The spatial position of the light varies on each trial and each correctly detected signal is rewarded with a food pellet. The second is the sustained attention task (SAT) developed by Bushnell and colleagues (Bushnell et al., 1994) and modified for visual attention by McGaughy and Sarter (1995). In the SAT, food- or water- deprived visual signals and blank trials are randomly presented. Responses are either hit or miss on cued trials, and correct rejection or false alarms on blank trials. Correct responses (hit or correct rejections) are rewarded and incorrect responses (misses or false alarms) initiate an intertrial interval without other consequences. In the SAT task, visual distractors can also be introduced to provide more challenging conditions (dSAT), and these characteristically impair detection of visual signals (Gill et al., 2000).

Rats in the dSAT first participate in a block of undistracted trials (about 50) before the distractors are presented. The distractor flashes at 0.5 Hz for 12 min, meaning that the 25 unpredictable signals are diluted among 360 false signals. Even after familiarization with the dSAT rats have elevated false alarms. Here increased false alarms can be reconceptualized as a prediction error as the predicted outcome of a reward is different than the actual outcome of no reward (Schultz and Dickinson, 2000). Following several false alarms, rats improve performance but are still relatively impaired. Thus, observations indicate that the rodent learns that reporting salient yet irrelevant light signals is a failing strategy, and then begin to actively filter out subsequent distractor flashes.

Loss of BFCS input to the cortex impairs performance in both the 5CSRTT (Muir et al., 1994) and the SAT (McGaughy et al., 1996; Bushnell et al., 1998; Chiba et al., 1999). Due to the role of PPC in visual attention in primates and the innervation of BFCS input to this region, parietal cholinergic deafferentation was attempted in both of these paradigms. Cholinergic deafferentation in the PPC did not produce any deficits in the standard version of the 5CSRTT (Maddux et al., 2007). However, in a Pavlovian overshadowing procedure rodents with cholinergic parietal lesions showed deficits in attention under conditions of prediction error or surprise.

Briefly, signals that provide partial reinforcement are more likely to prevent new learning, and signals that are consistently reinforced are more likely to form new associations with other signals (Pearce and Hall, 1980). Animals trained on the 5CSRTT with port signals that were either partially or consistently reinforced were then exposed to a pavlovian overshadowing task. Here, the port signals were paired with either a low or high tone. Although PPC ACh-lesioned animals performed normally on the 5CSRTT, they were impaired in the Pavlovian overshadowing task. This was consistent with previous studies showing specific loss of cholinergic input to the parietal cortex resulted in a failure to process conditioned stimuli that predict changes in the value of unconditioned stimuli, an effect interpreted as attention required for new learning (Chiba et al., 1995; Bucci et al., 1998; Maddux et al., 2007). This data has since been interpreted as demonstrating that the ACh reports a mismatch between bottom-up stimulus processing and top-down biasing and updates the contextual framework (Yu and Dayan, 2002, 2005; Bucci, 2009).

In a key experiment, St. Peters and colleagues used the dSAT to demonstrate the role of BFCS input to PPC processing (St. Peters et al., 2011). In that experiment, infusions of NMDA into the nucleus accumbens have no effect on standard SAT performance, but improve performance in the dSAT. Further, it was shown that cholinergic deafferentation of either PFC or PPC eliminated the performance-enhancing effects of intra-accumbal NMDA. Thus, this supports the hypothesis that cholinergic transmission in both the PFC and PPC is necessary for attentional effort required to

overcome challenging conditions, such as the presentation of distractors or compound signals (Sarter et al., 2006). The striatal component of this circuit is crucial for reporting performance errors, and has been discussed in detail elsewhere (Robbins and Everitt, 1996; Sarter et al., 2006).

Neurophysiological studies of the PPC in task performing rats provide evidence of how BFCS input modulates PPC neuronal activity. The presentation of relevant visual signals produces neurophysiological correlates of attention in rodent PPC. Rats were trained on a variant of the SAT and single unit and population activity from the PPC neurons are significantly activated by visual signals. Importantly, neurons were not activated on blank trials and missed signals, and only a small population of neurons was slightly activated by a visual distractor (Broussard et al., 2006). Further, when we recorded the local field potential in the PPC, a prominent P300 evoked response was found when relevant visual signals were presented and subsequently detected (Broussard and Givens, 2010; see below for more detail). Because the P300 is an event-related potential found on parietal sites in humans, this was further neurophysiological evidence of a rodent homolog of the PPC.

PPC RANKS ALLOCENTRIC SIGNALS IN A TEMPORALLY DYNAMIC MANNER TO GUIDE NAVIGATION

The PPC is also implicated in using external signals to navigate through space. There are two essential strategies a subject can follow for navigation. One can use the nearest landmarks available to determine the route and travel one landmark at a time. Portuguese sailors would travel along the coasts of Africa and Asia using this strategy. A subject can also use distant signals such as the sun and stars to judge their relative position. When the Portuguese sailed to Brazil, they relied on this strategy in the open seas. In psychological terms the use of local signals is called an *egocentric* strategy whereas the use of distant signals is called *allocentric*.

One test of egocentric navigation is an eight arm radial maze, where the experimenter places the subject in one arm and reward navigation only to adjacent arms. Here an egocentric strategy requires the subject to go to the nearest arm relative to the subject's initial position in the maze. If the subject begins each daily session in a different arm, it is difficult to use external signals to solve the maze. In this task, parietal lesions have no effect on performance (King and Corwin, 1992). One test of allocentric maze navigation is a cheeseboard task, requiring rodents to learn the position of a food reward on a large table with several recessed food wells. Here, the use of external signals is required to solve the maze. Rats with bilateral PPC lesions took longer paths and had more heading errors (i.e., they started in the wrong direction) than controls (King and Corwin, 1992). In rodents, egocentric signals are presented within a T-maze near the floor whereas allocentric signals are presented on curtains or walls outside of a maze. In rodents unilateral and especially bilateral PPC lesions produced deficits in allocentric navigation, while egocentric navigation remained intact (King and Corwin, 1992; McDaniel et al., 1995, 1998).

Studies investigating the neurophysiological correlates of navigation indicate that as a rodent travels through a path the navigational context dictates the firing pattern of PPC neurons (Chen et al., 1994a,b; Nitz, 2006). For example, if a rat learns to travel a specific route and reverses that route, then the firing pattern on the initial route is very different than the return route. In essence it could mean the temporal order of allocentric signals may influence how PPC ranks the relevance of that cue as the subject navigates through space. Deficits in navigation caused by parietal lesions may be a function of a more basic deficit in the ability of subjects to rank the relevance of external signals in the environment. Although this specific hypothesis has yet to be tested, the medial parietal cortex of human subjects is activated in a virtual reality maze when subjects travel novel, but not familiar, routes (Baumann and Mattingley, 2010). Thus, these basic attentional deficits may also translate into impairment in the ability to remember topological schemas using allocentric signals, a topic covered elsewhere (Goodrich-Hunsaker et al., 2008).

THE NEURAL CIRCUITRY INFLUENCING PARIETAL PROCESSING OF RELEVANT SIGNALS

PREFRONTAL-PARIETAL INTERACTIONS IN ATTENTION

Tasks requiring the filtering of distractors activate both PPC and frontal areas (Hazeltine et al., 2000; Marois et al., 2000; Lee et al., 2006). The activation of these two regions has been dissociated with progressive increases in attentional demand. Bunge and colleagues used a flanking distractor task, where congruent distractors flanking the target aided target detection, and incongruent distractors directed the subject to respond in an opposite manner relative to the target (2002). PPC areas were activated when both congruent and incongruent distractors were presented. Frontal cortex was only significantly activated on trials with incongruent distractors. The distinction here is important, and indicates that PPC actively processes spatial stimuli, and only those distractors that produce response conflicts (incongruent distractors misdirect subjects opposite the correct response) recruit PFC activation.

There is also neurophysiological evidence that PFC is involved in the suppression of distractors. Patients with PFC lesions have exaggerated evoked responses to irrelevant somatosensory and auditory stimuli (Yamaguchi and Knight, 1990). This effect was not replicated in patients with PPC lesions, and controls from this study indicate that the PFC directly suppresses sensory evoked responses. In contrast to this, Friedman-Hill and colleagues demonstrate that a patient with bilateral parietal lesions is impaired when required to filter out perceptually similar distractors, suggesting that the PPC does exhibit top-down selection of relevant visual signals (Friedman-Hill et al., 2003). Thus, the function of the PPC may not be to directly suppress the representation of distractors in sensory cortex, but to disengage from distractors when relevant signals are present (Posner and Petersen, 1990; Posner and Raichle, 1994, Chap. 7). The inability to dynamically rank competing stimuli may result in the impaired selection of relevant stimuli seen in these patients.

Nelson and colleagues (Nelson et al., 2005) investigated some of the mechanisms employed by PFC to modulate PPC activity. In this study perfusion of AMPA and the non-specific ACh agonist carbachol into the PFC increased ACh efflux distally in the PPC. Perfusion of nicotine and NMDA into the PFC did

not increase PPC ACh efflux, suggesting that muscarinic receptors in the PFC are necessary for PFC to elicit PPC ACh efflux. Perfusion of carbachol or nicotine throughout the PPC, while eliciting increases in local ACh efflux, failed to modulate PFC ACh levels. Moreover, local administration of AMPA into the PPC failed to elicit ACh efflux. These findings suggest PFC input to the BFCS can directly regulate parietal ACh levels. Importantly, PFC also directly projects to the locus coeruleus (LC) (Jodo et al., 1998), suggesting that PFC can modulate cortical levels of both NE and ACh. Thus, it can be proposed that distractors induce increases in prefrontal ACh that can subsequently recruit parietal ACh efflux in order to differentiate relevant and irrelevant signals (see **Figure 1**).

CHOLINERGIC MECHANISMS MEDIATING PARIETAL SIGNAL-TO-NOISE RATIO

Cholinergic neurotransmission has been shown to contribute to visuospatial attention in many paradigms (see earlier, also Botly and De Rosa, 2008). In the SAT, PPC neurons produced neurophysiological correlates of detection, and the hypothesis that cholinergic neurotransmission modulated parietal processing of signals was tested by locally infusing a selective cholinotoxin into the PPC of SAT-performing rats (Broussard et al., 2009). After collecting task-related neurophysiological control data, 192 IgG saporin was infused to deafferent cholinergic neurons projecting locally to PPC (Holley et al., 1994; Wenk et al., 1994). Importantly these were unilateral infusions in order to minimize possible confounding effects on performance.

In standard SAT conditions, PPC neurons from cholinergically deafferented animals are successfully recruited by the visual signal. However, cholinergically deafferention of PPC significantly more neurons responded to the distractor and significantly fewer responded to the signal. Lastly, signal-responsive neurons in deafferented PPC had a lower signal-to-noise ratio (SNR) compared to control conditions and intact subjects. The basal firing rate of these neurons was also elevated during the distractor block of the task. Thus, the cholinergic contribution to PPC processing of signals is hypothesized to provide a basal level of inhibition among local cortical assemblies within the PPC in order to filter distracting stimuli, enhancing the SNR to relevant signals.

As mentioned earlier, the distractor increases the FA rate, producing in several prediction errors that are hypothesized to recruit increased *attentional effort*. The PFC monitors increases in prediction errors and activates cholinergic signals to normalize the SNR of PPC neurons and filter out task-irrelevant signals (Sarter et al., 2006). The dSAT also elevates PPC cholinergic efflux above

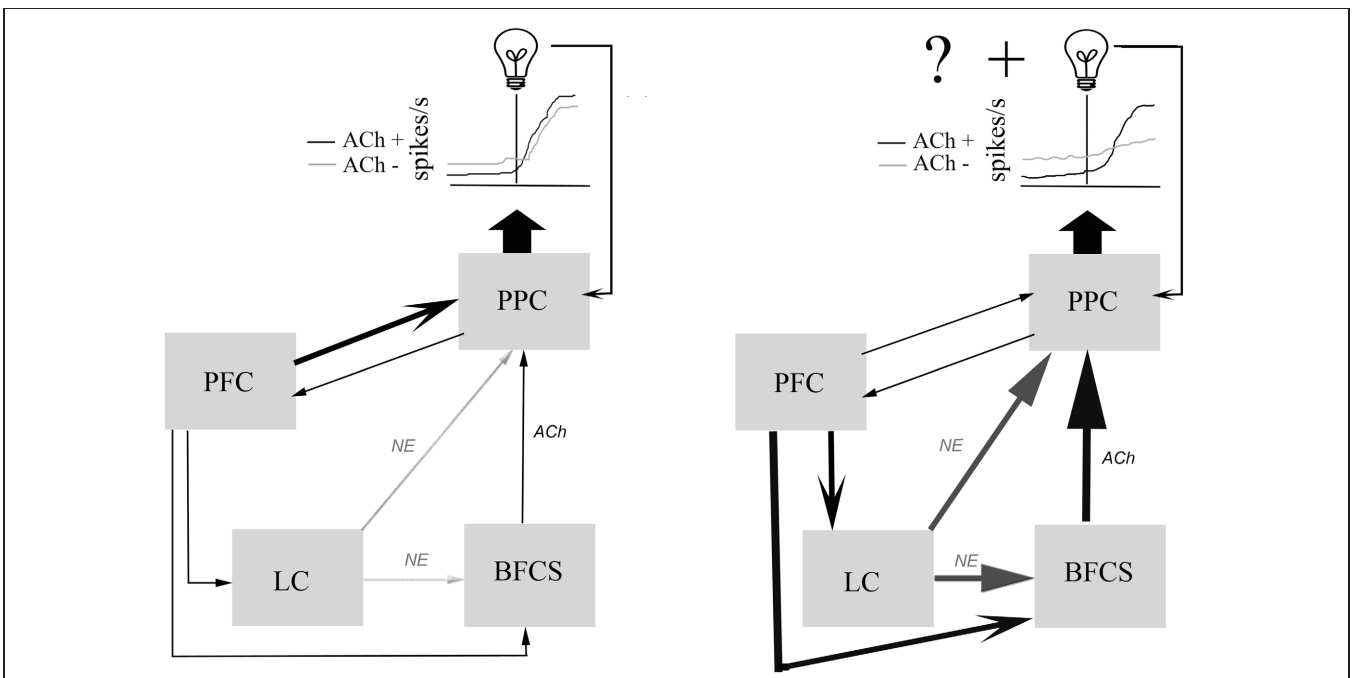

FIGURE 1 | Schematic diagram illustrating the main components of a neuronal network mediating the posterior parietal cortical (PPC) processing of relevant sensory signals. *Left*, Signals that are well-learned to reliably predict specific outcomes (as represented by the light bulb) require an interaction between frontal, parietal, and sensory cortices to bias the detection and selection of these sensory signals in order to direct proper responses. Neurons in the PPC integrate this input and fire action potentials, represented by the idealized raster plots. Here, neuromodulatory tone from noradrenergic and cholinergic centers only weakly contributes to PPC processing of signals and intact (ACh+) and cholinergically deafferented subjects (ACh–) have similar responses to relevant signals (Broussard et al., 2009). *Right*, Changes in the ability of learned signals to predict results, either through changes in cue identity, dilution of the signal with intramodal distractors, loss of response contingency, or reversal of response rules will produce prediction errors. In order to overcome these increased errors a motivated subject will require active frontal systems (PFC) to recruit increased cortical neuromodulatory tone (Sarter et al., 2006). The dilution of a visual signal with intramodal distractors unmasks the cholinergic contribution to PPC processing of visual signals. Loss of cholinergic input to the PPC under distractor conditions produces an elevated basal firing rate, and a decreased representation of the visual signal resulting in a reduction in the signal-to-noise ratio.

normal SAT performance; further evidence of cholinergic influence over PPC processing in the face of challenges requiring attentional effort (Himmelheber et al., 2001; Sarter et al., 2006; St. Peters et al., 2011). This is consistent with the observation in human subjects performing a cued target detection task (Thiel et al., 2005; Giessing et al., 2006; Thiel and Fink, 2008). Here subjects fixate on a central cue that covertly directs them to the right or left visual field. Shortly thereafter, a target appears in either the right or left side and the subject must report detection by pushing a button. Valid cues produce a faster reaction time than invalid cues, a phenomenon known as the "validity effect" (Posner, 1980). Nicotine reduces the validity effect by reducing the reaction time and PPC activity on invalid trials (Thiel et al., 2005; Thiel and Fink, 2008). These effects can be interpreted as an inhibition of the parietal processing of signals with low predictive certainty. Muscarinic neurotransmission is also important as local infusions of scopolamine into the PPC impaired the performance of monkeys on a similar attention task (Davidson et al., 1999).

On a rodent version of the cued target detection task, loss of cortical cholinergic input resulted in decreased accuracy and increased reaction time in response to invalid cues (Bushnell et al., 1998; Chiba et al., 1999). Taken together, this evidence supports the hypothesis that cholinergic input contributes to parietal ranking of the relevance of signals, as increased nicotinic activity discounts processing of low predictive signals and a lack of cholinergic input results in a perseverant processing of invalid signals. Evidence from parietal neurophysiological studies suggests that the cholinergic effects on parietal SNR also influence the validity effect.

The enhancement of the SNR of parietal neurons is consistent with findings of several studies recording evoked responses from brain slices and anesthetized preparations. Application of cholinergic agonists or stimulation of basal forebrain cholinergic nuclei enhanced the cortical responsiveness to sensory stimuli in visual cortex (Sillito and Kemp, 1983; Roberts et al., 2005; Herrero et al., 2008; Roberts and Thiele, 2008; Goard and Dan, 2009), auditory cortex (Metherate et al., 1990), and somatosensory cortex (Alenda and Nunez, 2007). Studies in awake animals demonstrated that the auditory evoked response (Berntson et al., 2003b) of rats to arousal generating stimuli is significantly reduced following loss of cortical cholinergic input. Recordings from brain slices of the anterior cingulate cortex (McCormick and Prince, 1986) demonstrated that exogenous application of ACh produced an initial, phasic hyperpolarization of neurons followed by a tonic depolarization. Focal application of ACh produces a transient inhibition of prefrontal, somatosensory, and visual cortical pyramidal neurons. This effect is produced by activation of M1-like muscarinic receptors. Muscarinic neurotransmission releases calcium from intracellular stores, in turn activating calcium activating potassium channels (SK) (Gulledge and Stuart, 2005; Gulledge et al., 2007). Cortical neurons can inhibit processing from neighboring neurons while enhancing the processing of sensory stimuli within a specific window of time through this general mechanism (Hasselmo and Sarter, 2011).

Current theoretical models regarding the modulation of sensory processing by ACh are broadened by integrating the contributions of both muscarinic and nicotinic receptor subtypes. Zinke and colleagues (2006) proposed that ACh reduces lateral cortical integration by acting on M2 receptors that are typically bound presynaptically to local interneurons (Mrzljak et al., 1996; Kimura, 2000). Nicotinic α4β2 receptors facilitate presynaptic glutamate release from the thalamocortical afferents (Hasselmo and Bower, 1992; Vidal and Changeux, 1993; Gioanni et al., 1999). Although this evidence is derived from primary visual cortex, this could be a general mechanism that ACh employs to produce a shift in cortical processing from local cell assemblies to heightened thalamocortical processing, a shift that may play a role in signal detection (Hasselmo and McGaughy, 2004; Sarter et al., 2005).

A recent study characterized the inhibition of unitary (i.e., one synapse) cortico-cortical connections in the presence of carbachol and nicotinic agonists (Levy et al., 2006). Recordings from somatosensory cortex *in vitro* indicated that when a layer 5 pyramidal cell was stimulated, neighboring cortical cells $<100\,\mu m$ away generated excitatory post-synaptic potentials (EPSPs). In the presence of non-specific ACh agonist carbachol, the EPSP of cells neighboring the stimulated neuron was reduced, an effect that was blocked by muscarinic antagonists atropine. Further investigation showed that blocking M2 receptors was more effective than blocking M1 receptors in reversing the carbachol-induced suppression. Nicotinic agonists reduced unitary EPSPs only in the absence of Mg^{2+}, suggesting that only in the presence of stimulation significant enough to unblock NMDARs would induce unitary intracortical suppression.

In conclusion, evidence investigating the mechanisms of ACh modulation of cortical responsiveness supports the general hypothesis that ACh increases the signal-related responses of cortical neurons relative to the background firing rate (i.e., the "SNR"). Importantly, in recordings from PPC neurons, cholinergic deafferentation was reduced during distractor sessions, suggesting that cholinergic neurotransmission may facilitate the filtering of distracting stimuli.

NORADRENERGIC MODULATION OF SENSORY PROCESSING

In addition to the contribution of the cortical cholinergic system to stimulus detection and response selection, a general increase in arousal may be required for a subject to counteract unexpected violations of prior expectations. The LC, the main cortically ascending NE nuclei, projects throughout the cortex, including the PPC (Kobayashi et al., 1974; Descarries et al., 1977), and stimulation of the LC produces NE efflux in both the PPC and PFC (Devoto et al., 2005). NE input to the PPC is dense, and NE input to BF nuclei may contribute to further elevated levels of ACh. The specific contribution of ascending NE inputs to rodent PPC has not been studied, but a prevalence of primate and human studies support the notion that NE contributes to shifts in attention. Neurons in the LC are activated shifts in visual attention and are hypothesized to guide the response late in the decision-making process (Clayton et al., 2004).

In rodents, the dissociation of the roles of cholinergic and NE modulation to attentional processing was exemplified in a study by Dalley and colleagues (Dalley et al., 2001). Here, microdialysis probes implanted in rats revealed that normal 5CSRTT performance elevates cholinergic, but not NE levels in the prefrontal

cortex. This was consistent from day to day, i.e., the task was well-learned and increases in acetylcholine were resistant to overtraining. In contrast, in rats whose rewards were contingent upon another rats' performance (yoked) increased NE efflux. This effect lasted on the day the contingency was yoked; subsequent sessions did not elevate NE levels. Cortical-wide depletions of NE, but not ACh, impairs performance on attentional set-shifting tasks when the relevant cue shifted dimensions (McGaughy et al., 2008). In addition to this direct neuromodulatory influence on cortical processing, the LC projects to the basal forebrain where it may selectively bias the processing of anxiogenic stimuli (Hart et al., 1999; Berntson et al., 2003a,b). Whether NE contributes to parietal processing of targets in the 5CSRTT or SAT remains an open question.

Based on these and other findings, cholinergic neurotransmission within the cortex is thought to mediate *expected uncertainty,* i.e., defined as known degree of unreliability of predictive signals within a given environment. NE neurotransmission within the cortex is thought to compensate for *unexpected uncertainty*, when global changes in cue identity or task rules violate prior expectations (Yu and Dayan, 2005). A recent modeling simulation exemplifies this concept (Avery et al., 2012). In it a subject is placed in a circular field surrounded by 36 lights each 10° apart. On any trial a light directs a simulated rodent to a port, and the subject is required to break a light beam in the lit port and return to the center for a reward. In this paradigm the experimenter controls the mean and standard deviation of the relevant light. Within a fixed number of trials, the mean (from 0 to 360°) and standard deviation remain fixed so that an expected range of relevant lights can be monitored. This reflects the degree of *expected uncertainty* in the paradigm. After a fixed number of trials the experimenter shifts the mean, violating prior expectations set by previous trials; this represents *unexpected uncertainty*. In this biologically based model phasic bursts of ACh track small deviations from the mean signal presentation region, whereas bursts of NE track global changes in the mean. As valuable as these modeling data are, there are few studies that investigate the role of NE specifically in PPC, and it is yet to be determined whether NE efflux in the PFC alone is sufficient to overcome enhanced *unexpected uncertainty*.

Another unresolved issue is that it is yet to be determined whether distractors present *expected* or *unexpected uncertainty*. The SAT, as mentioned earlier, elevates cortical ACh (Arnold et al., 2002), i.e., in turn further elevated by distractors (St. Peters et al., 2011). This and other findings have been the basis of the construct attentional effort that require a motivated subject must allocate additional attentional resources to overcome challenges (Sarter et al., 2006). But in this paradigm the distractor does not violate the predictive validity of a cue, but it does dilute the relevant signal with several false signals. It would be interesting to test the hypothesis that distractor-related increases in cortical ACh are a function of elevated NE drive to BFCS [see Figure 3 of Sarter et al. (2006)].

Some of the mechanisms underlying NE influence on cortical processing have been studied. NE neurotransmission via beta receptors modulates the responsiveness of sensory neurons. Specifically, stimulation of rodent whiskers at levels that do not activate barrel cortex is enhanced when the stimulation frequency of the LC is increased. This increase in stimulation frequency represents a change in the firing rate of the LC and it is proposed that this elevates cortical NE, enhances the sensory processing of subthreshold stimuli (Devilbiss and Waterhouse, 2004).

PARIETAL LOCAL FIELD POTENTIALS IN SAT-PERFORMING ANIMALS

Extensive reviews focusing on the distinction between unit activity and LFP activity have been published (Logothetis, 2003; Buzsaki, 2006). Single unit recordings measure the extracellular field potential when microelectrodes are placed close to the soma or axons of a neuron, and reports the action potentials produced by the nearest population of neurons. The firing rate of neurons has been a critical measure for comparing the neural activity of sensory processing or behavior for decades (Mountcastle et al., 1975; Boudreau et al., 2006). Measuring single unit activity provides no information about subthreshold inputs to dendritic arbors or integrative processing in the soma.

By contrast, LFPs represents the cooperative activity of neural populations. Rhythmic LFPs of high amplitude and low frequency, classified originally in the EEG literature as delta and theta oscillations, and are generated by the interaction of thalamocortical and neocortical activity and are typically modulated by the ascending neurotransmitter systems, such as ACh, NE, and histamine (Steriade et al., 1993; Eggermann et al., 2001; Lee et al., 2005).

Studies that simultaneously measure single unit and LFP activity demonstrated that the firing rate of single neurons can be gated in part by the oscillations in the local field (Costa et al., 2006). When the local extracellular field is positive, neurons embedded within the field are inhibited; as the intracellular milieu approaches threshold potential the conditions are more favorable to local cell firing. Conversely, as the local extracellular field is negative, it can lower the firing threshold of neurons embedded within that field, thereby temporally constraining the firing of neurons.

There are several measures of the field potential that correlate with either bottom-up processing of salience or top-down biasing of choices. One such measure is the P300 response, a positive extracellular potential that peaks around 300 ms post signal in humans. In terms of the classic EEG literature the P300 is a single, high amplitude cycle of the delta oscillation (Polich, 2007), that has a maximal amplitude in humans and primates at parietal sites (Linden, 2005). The standard paradigm used to generate the P300 response is the "oddball task," where infrequent targets are successively presented with frequent targets of varying relevance. The amplitude of the P300 varies as a function of stimulus discriminability, and was also found in rats (Broussard and Givens, 2010). In the SAT, short duration signals and distractors did not produce a P300 response. However, highly salient 500 ms signals produced a considerable P300 response from SAT-performing rats.

Another component of the field potential related to task performance is the long-latency (500–1000 ms post signal) contingent negative variation (CNV). The CNV was first measured from the scalp of humans and has two components. The first component is generated in anterior areas over the frontal eye field

and is developed after a stimulus calls for a decision. The second component is found over more central areas and is related to the execution of a prepared response plan (Singh et al., 1990). In PPC, the CNV is more likely to correspond to central generation of the CNV and reflect correct responses to targets (Le Dantec et al., 2007). In SAT-performing rats recording from PPC LFP revealed a detection-specific CNV. Unlike the P300, the CNV-like response in rat PPC was the same regardless of signal duration (Broussard and Givens, 2010). The CNV correlated with an increasing alpha power and an increase in firing rate of PPC neurons in SAT-performing rats. It must be reiterated here that neither CNV-like responses nor phasic increases in firing rate occurred on non-signal trials, indicating that these events underlie an effortful processing of a signal preceding a response.

Because the P300 is an extracellar positive potential, it is hypothesized that it is a wave of inhibition that sweeps throughout the PPC, minimizing local cortico-cortical activity (Polich, 2007). This ongoing activity may reflect the maintenance of a response plan in working memory. In the SAT task, rats perform better on high-probability on non-signal trials, and SAT-performing rats have been shown to position themselves near the non-signal response lever. This evidence supports the hypothesis that rats maintain a non-signal response plan in working memory during the intertrial interval. Phasic cholinergic signaling here may also contribute to facilitate nicotinic currents influencing thalamocortical circuitry, resulting in increased firing rate of PPC neurons prior to proper responding on signal trials. Muscarinic receptor neurotransmission acting on a slower timescale (seconds to minutes) can lower the baseline firing rate on subsequent trials. Muscarinic and NE signaling acting at this timescale could also potentiate the P300 response, phasically inhibiting local parietal cell assemblies and facilitating a shift to thalamocortical processing. Then, the extracellularly negative CNV potential could act to disinhibit PPC activity to maintain sensory-driven neuronal spiking generated by specific PPC neurons.

WORKING MODEL/CONCLUSIONS

To summarize, the PPC is hypothesized to be a necessary component of an attentional network comprised of PFC, thalamus, striatum, and neuromodulatory influence from ascending cholinergic and NE nuclei. Parietal neurons fire in response to behaviorally relevant stimuli but only when subjects report that they have detected them (i.e., not on miss trials). When attentional demands and uncertainty levels are static, neuromodulatory influence may not be necessary for parietal processing of signals. However, presenting distractors, novel compound stimuli, or other task manipulations requiring new learning recruit's increases in neuromodulatory tone to dynamically update associations within the PPC by modifying the firing rate and thus the ranking of these signals. Cholinergic input may be recruited in conditions of elevated expected uncertainty, such as when a subject must monitor and consciously ignore known distractors and attend to behaviorally relevant signals. Cholinergic signaling may act through nicotinic receptors at rapid timescales to facilitate thalamocortical processing and muscarinic receptors at slower timescales to inhibit local recurrent cell assemblies, in doing so lower the basal firing rate of parietal neurons and enhance the SNR of their response to relevant signals. The contribution of NE input to parietal attentional processing is less clear, but models suggest that NE efflux facilitates inhibition within the cortex, contributing for example to the globally inhibiting P300 response. Also, projections from LC to the BF serve to further elevate cortical ACh under conditions requiring additional attentional effort. The inhibition facilitated by the influence of NE and ACh on local circuitry within the PPC may act to clear the contents of working memory and bias parietal neurons in favor of processing incoming signals so as to generate the optimal behavioral response.

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Representation of numerosity in posterior parietal cortex

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Humans and animals appear to share a similar representation of number as an analog magnitude on an internal, subjective scale. Neurological and neurophysiological data suggest that posterior parietal cortex (PPC) is a critical component of the circuits that form the basis of numerical abilities in humans. Patients with parietal lesions are impaired in their ability to access the deep meaning of numbers. Acalculiac patients with inferior parietal damage often have difficulty performing arithmetic (2 + 4?) or number bisection (what is between 3 and 5?) tasks, but are able to recite multiplication tables and read or write numerals. Functional imaging studies of neurologically intact humans performing subtraction, number comparison, and non-verbal magnitude comparison tasks show activity in areas within the intraparietal sulcus (IPS). Taken together, clinical cases and imaging studies support a critical role for parietal cortex in the mental manipulation of numerical quantities. Further, responses of single PPC neurons in non-human primates are sensitive to the numerosity of visual stimuli independent of low-level stimulus qualities. When monkeys are trained to make explicit judgments about the numerical value of such stimuli, PPC neurons encode their cardinal numerical value; without such training PPC neurons appear to encode numerical magnitude in an analog fashion. Here we suggest that the spatial and integrative properties of PPC neurons contribute to their critical role in numerical cognition.

Keywords: posterior parietal cortex, number, human, animal cognition, electrophysiology, psychophysics

Humans possess a deep understanding of the meaning of numbers, and the practical use of this abstract ability is ubiquitous. We rely on numerical information in a myriad of daily tasks ranging from the simplicity of purchasing a cup of coffee to the complexity of developing financial instruments like mortgage-backed securities—irrespective of the wisdom of doing so. Complex quantitative behaviors are not limited to humans. Even the apparently simple behavior of a bee collecting pollen from a flower involves the computation and comparison of relative rates of return from various patches of flowers (Couvillon and Bitterman, 1985; Montague et al., 1995; Shapiro et al., 2001). A wealth of research suggests that humans share with animals a representation of number as an analog magnitude on an internal, subjective, scaled "number line" that is less precise with increasing magnitude (Platt and Johnson, 1971; Whalen et al., 1999).

However, there are several considerations that may constrain the instantiation of such a numerical scaling in neural circuits. For example, it remains hotly debated whether small numbers (one-two-three) are represented in a qualitatively different manner than larger estimated numerosities (Hyde, 2011). Moreover, the neural signatures of numerical judgments must be compatible with the manner in which an analog magnitude system estimates quantity. Ultimately, the representation of quantity must be stripped of the continuous properties of that which is quantified, e.g., "six" has the same meaning whether it describes six drops of water or six beluga whales. Psychophysical measurements provide limits as to the properties that must be accounted for by the neural systems that represent quantity. One concept of such a number line could be more literal, akin to an orderly spatial map of quantity in the brain (Dehaene et al., 1993; Gut et al., 2012). Here, we take a broader view that the properties of numerical cognition evident from behavior emerge from the response properties of neurons in parieto-frontal circuitry, in which posterior parietal cortex (PPC) plays a crucial role.

PSYCHOPHYSICS OF NUMERICAL DISCRIMINATION

Psychophysical data suggest that number is represented as a point on an analog mental number line. For example, rats or humans asked to produce n responses or estimate n events do so with less precision as n increases (Platt and Johnson, 1971; Whalen et al., 1999). In addition, the variability of responses increases proportionally with n such that the coefficient of variation (CV, the ratio of the standard deviation to the mean) is constant as n increases. Indeed, members of the Piraha tribe of Amazonia, whose numerical language is limited to

"one-two-many," show a similar pattern of behavior in which both the number and variability of numerical estimates increase with *n*, with a constant CV (Gordon, 2004). The similarity between animals and humans, even those using innumerate language, suggests a common underlying system for numerical estimation.

Hallmarks of numerical comparison are the distance and magnitude effects. Humans reporting the larger of two numbers do so faster and more accurately as the distance between them increases. And, when the distance between two numbers is fixed, accuracy and speed decrease as the overall magnitude of the two numbers increases (Moyer and Landauer, 1967). Thus, subjects more accurately and quickly discriminate 2 vs. 9 than 6 vs. 7 (distance effect) or 32 vs. 39 (magnitude effect). Distance and magnitude effects are also found in the accuracy and reaction times of monkeys and pigeons ordering pairs of numerosities (Brannon and Terrace, 1998, 2000; Nieder and Miller, 2004a; Scarf et al., 2011). **Figure 1** shows the similar ratio-dependence in the accuracy and speed of monkeys and humans reporting which of a pair of numerosity stimuli contains more (or fewer) elements (Cantlon and Brannon, 2006). These behavioral findings endorse the idea that the internal representation by the mental number line has greater variability with increasing quantity. Such a number line could be logarithmically compressed or linear with scalar variability (Brannon et al., 2001; Dehaene, 2001).

Performance of simple approximate arithmetic tasks suggests that these operations are carried out using an analog representation of quantity. Participants who cannot rely on the rote memorization of basic mathematical operations (such as $2 + 3 = 5$) nevertheless demonstrate the ability to perform simple calculations. Pre-schoolers accurately report whether the sum of two arrays of dots contains a larger number than a comparison array (Barth et al., 2006) and monkeys can choose a visual array that matches the sum of two sample arrays (Cantlon and Brannon, 2007). Even pigeons can discriminate the result of a subtraction operation from a constant value (Brannon et al., 2001; Dehaene, 2001). The Munduruku tribe of Amazonia, which lacks language for quantities greater than five, can estimate the results of approximate addition and subtraction, as well as compare quantitative stimuli well beyond their range of numerical literacy (Pica et al., 2004). Further, in these studies, accuracy for mathematical operations depended on the ratio of quantities compared. These findings suggest that mathematical operations are computed over a representation of quantity that is either linear with scaled variability or logarithmically compressed.

A critical prediction of Weber's law is that the ratio of two numbers determines their discriminability, regardless of their actual magnitude. Several lines of evidence using tests of non-symbolic numerical processing suggest number is innately represented on a compressed analog scale that supports ratio-dependence in discriminations. Human infants have been shown to discriminate large numbers, provided they differ by a ratio of 2:1, e.g., 8 vs. 4 or 16 vs. 8 (Xu and Spelke, 2000; Lipton and Spelke, 2003; Wood and Spelke, 2005). Adult human discrimination of non-symbolic visual arrays has also been shown to depend on the ratio of values compared, rather than their absolute magnitude (Piazza et al., 2004, 2007). A potential advantage of compressed scaling is the ability to process a wide range of quantities, just as the visual or auditory systems can process stimuli differing over orders of magnitude.

In studies of non-verbal subjects, such as animals and human infants, the confounding relationship between number and other stimulus attributes makes it difficult to demonstrate the capacity to represent number *per se*. For example, choices based on

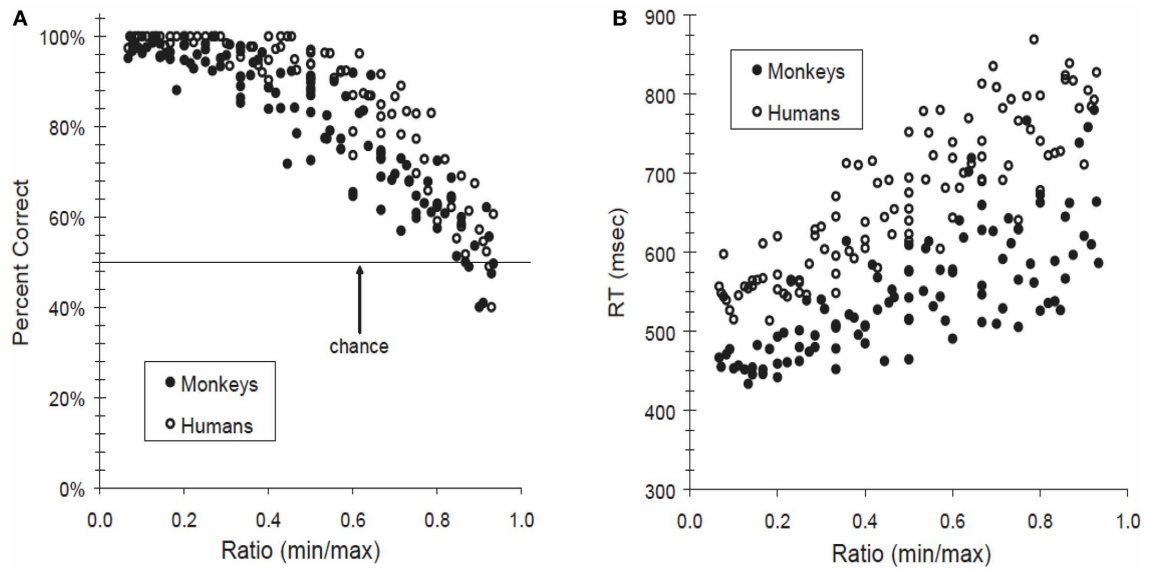

FIGURE 1 | Humans' and monkeys' judgments of relative numerosity (more/fewer) depend on the ratio difference between the two stimuli. When judging arrays of dots that differ in quantity, accuracy increased **(A)** and response time decreased **(B)** as their ratio deviated from 1. For example, discrimination performance for 2 vs. 10 (ratio = 0.2) was faster and more accurate than for 9 vs. 10 (ratio = 0.9). From Cantlon and Brannon (2006).

simultaneously presented stimuli that differ in number could be determined on the basis of such features as total surface area or density whereas the discrimination of sequentially presented stimuli, or production of a series of *n* responses, could be controlled by duration (of individual elements or the entire series) rather than number. More generally, number, space, and time all show similar properties of discriminability that follow Weber's law (Walsh, 2003), thus it is difficult to disentangle judgments based solely on numerosity apart from spatial and temporal magnitudes. Although animals are able to use number, it is possible that they do so only as last resort (Davis and Perusse, 1988). This proposition seems unlikely since both humans and animals performing tasks that do not oblige them to represent number do so (Meck and Church, 1983; Roberts and Mitchell, 1994; Brannon and Terrace, 1998; Roitman et al., 2007a; Jordan et al., 2008). Number thus appears to be spontaneously encoded, even when it is redundant with other cues.

NEUROBIOLOGY OF NUMERICAL REPRESENTATION

Neurological and neurophysiological data indicate that parietal cortex is a critical component of the circuits that form the basis of numerical abilities in humans. Patients with parietal lesions are impaired in their ability to access the deep meaning of numbers. Acalculiac patients with inferior parietal damage often have difficulty performing arithmetic (2 + 4?) or number bisection (what is between 3 and 5?) tasks, but are able to recite multiplication tables and read or write numerals (Dehaene and Cohen, 1991, 1997; Cohen and Dehaene, 1994). Gerstmann syndrome, which is characterized by the tetrad of acalculia, left-right disorientation, finger agnosia, and agraphia, is found in patients with inferior parietal damage (Gerstmann, 1940; Roeltgen et al., 1983; Benton, 1992). The progress of Gerstmann syndrome onset in Alzheimer's disease patients suggest that the degeneration underlying these four cognitive impairments share anatomical proximity in the parietal lobe (Wingard et al., 2002). Further, Turner's syndrome, an X-linked chromosomal disorder in humans, is marked by both structural abnormalities of the intraparietal sulcus (IPS) and abnormal development of numerical representation (Molko et al., 2003).

Complementary data from fMRI studies of neurologically intact humans performing subtraction (Simon et al., 2002), number comparison (Pinel et al., 2001), and non-verbal magnitude comparison (Fias et al., 2003) tasks show activity in the IPS. Taken together, clinical cases and imaging studies support a critical role for parietal cortex in the mental manipulation of numerical quantities. More specifically, Simon et al. (2002) suggest that the functional organization of human parietal lobe resembles that found in monkeys (Rizzolatti et al., 1998), and propose that correlates of numerical processing in primates may be found in areas along the IPS.

Studies of the role of parietal cortex in non-symbolic numerical representation in humans have produced conflicting data. Imaging studies have consistently reported the activation of parietal cortex in the processing of symbolic number, i.e., number words or Arabic numerals (Dehaene and Cohen, 1997; Pinel et al., 2001; Simon et al., 2002). To test whether representation of number in parietal cortex extends to non-symbolic stimuli, Piazza et al. (2004) employed an fMRI adaptation paradigm. In that study, human participants passively viewed visual arrays of *n* elements. As subjects habituated to a standard number (16 or 32), deviant values, ranging from half to double the value of the standard, were presented infrequently. Although participants were not explicitly required to discriminate the visual stimuli in any way, recovery of the BOLD signal along right and left IPS was proportional to the ratio of the standard and deviant stimuli (**Figure 2**). The same regions did not respond to changes in the shape of the elements. Further, adaptation to repeated numerosities and recovery in response to a deviant numerical value did not depend on whether non-symbolic (arrays of dots) or symbolic (Arabic numerals) stimuli were used (Piazza et al., 2007). Thus, brain activation by deviant numerical stimuli followed Weber's law. Subsequent studies not only replicated the adaptation of regions along the IPS to non-symbolic visual stimuli, but extended these findings to proportions (Jacob and Nieder, 2009). Subjects habituated to arrays of elements in which 50% (of totals ranging from 4 to 32) were colored blue and the rest were red. Infrequent probes with deviant stimuli composed of 60–90% red items drove recovery of the BOLD signal, with

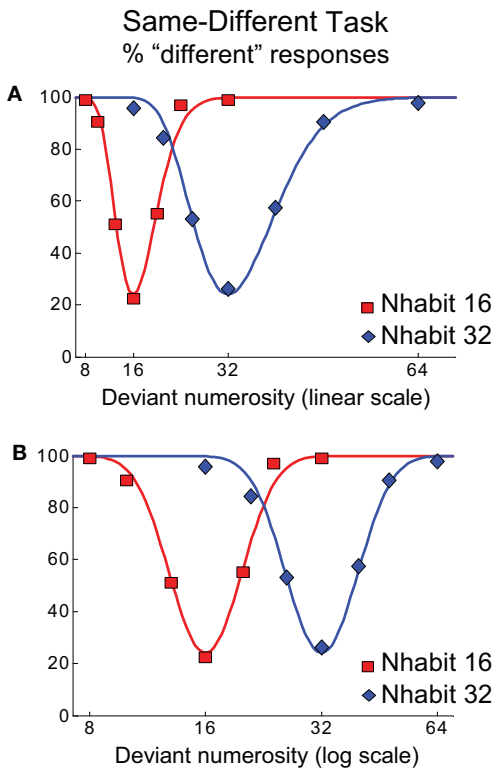

FIGURE 2 | Areas along the horizontal intraparietal sulcus showed activation in response to a change in the numerosity of sequentially presented visual stimuli. The level of activation was proportional to the magnitude in the change of numerosity from a habituated standard value (16 or 32). The discriminability of probe values relative to the standard is compressed on a linear scale **(A)**, and symmetrical on a logarithmic scale **(B)**, consistent with Weber's law. Reprinted with permission from Piazza et al. (2004).

greater recovery as the distance between habituation and deviant proportion increased. Thus, regions along the IPS not only appear to encode estimates of whole numbers, but proportions as well.

Counter to the suggestion that dedicated circuitry in parietal cortex is responsible for processing symbolic and non-symbolic quantity, Shuman and Kanwisher (2004) did not find adaptation of parietal responses to repeated presentations of non-symbolic numerical stimuli. Although they found greater IPS activation for difficult non-symbolic numerical comparisons, similar patterns of activation were observed for difficult color comparisons, suggesting that activation of this region is not limited specifically to the number domain. Ongoing research using electrophysiological methods (described below) similarly suggests that broader functions of parietal cortex support numerical cognition.

The earliest findings of a neural representation of number in animals also suggested a role for parietal cortex. Neurons in parietal cortex in anesthetized cats responded to the n^{th} stimulus in a series, regardless of modality or inter-stimulus interval (Thompson et al., 1970). In monkeys, parietal neurons in area 5 were shown to respond to repetition number in a sequence of arm movements (Sawamura et al., 2002). These neurons had somatosensory receptive fields, but approximately one-third of the neurons studied had activity that was also modulated in relation to the position of the movement in a sequence. When inactivated, monkeys were impaired in completing the number of required repetitions of movements accurately, suggesting that these neurons were required to track the number of movements completed (Sawamura et al., 2010). Although the majority of studies related to neural encoding of quantity focus on regions within parietal cortex that process visual and oculomotor function, the work of Sawamura and colleagues shows similar encoding of quantity in circuits that process somatosensory information in arm movements.

The strongest evidence for neural correlates of numerical quantity has been found in the activity of single neurons in PPC of macaque monkeys judging visual stimuli varying in numerosity. PPC has been implicated in higher order sensorimotor processing and while not primarily sensory or motor in function, receives inputs from multiple sensory modalities and influences movement planning. There are several characteristics of PPC neurons that have implications for our interpretation of how quantity may be encoded at the level of single neurons. The areas along the IPS are considered to be part of the dorsal visual pathway carrying information about the location and movement of objects, and guiding eye or hand movements toward those objects in space (Ungerleider and Mishkin, 1982). The ventral intraparietal area (VIP), located in the fundus of the IPS, is situated to process visual and somatosensory information via inputs from the middle temporal (MT) and medial superior temporal (MST) visual areas, and from somatosensory areas 5 and 7 of the superior parietal lobule (Seltzer and Pandya, 1986; Ungerleider and Desimone, 1986; Boussaoud et al., 1990; Duhamel et al., 1998). Neurons in the lateral intraparietal area (LIP), in the lateral bank of the IPS, also receive inputs from visual motion areas MT and MST, but are driven by auditory stimuli as well (Felleman and Van Essen, 1991; Mazzoni et al., 1996b; Mullette-Gillman et al., 2005). Area LIP is interconnected with areas involved in the generation of saccadic eye movements, such as the superior colliculus and frontal eye field (Baizer et al., 1991). Anterior to LIP along the lateral bank of the IPS is the anterior intraparietal area (AIP), which responds to both visual stimuli and grasping movements of the hand (Jeannerod et al., 1995; Sakata et al., 1995). Intraparietal neurons are thus ideally situated to organize perception of multimodal stimuli toward appropriate behavioral responses.

A defining trait of neurons along the IPS is their spatially selective response fields (RF). These neurons respond to stimuli presented in Colby et al. (1996) and/or movements directed toward (Barash et al., 1991; Mazzoni et al., 1996a) a restricted area of space, typically in the contralateral hemi-field. The spatial selectivity of parietal neurons is modulated by a variety of task parameters, such as the salience of visual stimuli (Colby and Goldberg, 1999), motor planning (Snyder et al., 1997), decision-making (Shadlen and Newsome, 2001), categorization (Freedman and Assad, 2006), reward expectation (Platt and Glimcher, 1999; Sugrue et al., 2004), social expectations (Klein et al., 2008), and elapsed time (Leon and Shadlen, 2003). In addition, responses of parietal neurons can be affected by non-spatial information such as shape and color (Sereno and Maunsell, 1998; Toth and Assad, 2002), as well as information located outside of the classical RF (Freedman and Assad, 2009).

Neurons in PPC were first shown to encode the cardinal value, e.g., "4," of visible objects in monkeys performing a delayed-match-to-sample task (Nieder and Miller, 2004b). On each trial, a sample stimulus containing 1–5 elements was presented, followed by a delay period in which no stimuli were visible. After the delay, a test stimulus containing either the same number of elements or a set that differed by one element was presented. The locations of the elements were randomized around a central fixation point, and monkeys reported when the test stimulus matched the sample by releasing a lever. Thus, the spatial configuration of the stimuli was not matched to the RFs of neurons studied, and the motor response did not have a spatial component such as a reach or eye movement to a particular target. The area, circumference, arrangement, density, and shape of the items in the numerosity stimuli were systematically varied to ensure that number alone was the basis for a match. Consistent with standard magnitude effects on numerical performance, behavioral response accuracy declined as the number of items in the sample increased. In an additional set of behavioral experiments where the sample and test stimuli differed by more than one element, performance improved as the difference between the sample and test stimuli increased (Merten and Nieder, 2009). The performance of monkeys in this task thus demonstrated distance and magnitude effects like those seen in Brannon and Terrace (1998, 2000).

While monkeys performed the delayed-match-to-numerosity task, the activity of randomly selected neurons in prefrontal and PPC was measured. For approximately one-third of neurons in prefrontal cortex (PFC), ∼20% of neurons in the fundus of the VIP, and ∼10% of neurons in the lateral bank of the intraparietal sulcus (LIP), activity measured during the presentation of the sample stimulus or the delay period was maximal for one quantity

and declined as distance from that quantity increased. "Tuning" curves for numerosity were broader as numerosity increased from 1 to 5, suggesting a possible correlate of numerical distance and magnitude effects (Nieder et al., 2002; Nieder and Miller, 2003). **Figure 3** shows an example of a single neuron with tuned for the preferred value of "3." For numerosities up to 30, individual PFC neurons preferred a particular value, with tuning curves better fit by logarithmic rather than linear scaling (Nieder and Merten, 2007). The onset of numerical discrimination by parietal neurons preceded that of prefrontal neurons by ∼30 ms, suggesting that quantity is initially encoded in PPC then passed to PFC for task-related processing (Dehaene, 2002; Nieder and Miller, 2004a).

In addition to coding the quantity of elements in simultaneously presented numerical arrays, VIP neurons show similar preferences for a preferred ordinal position in a numerical sequence, i.e., respond best to the second stimulus, regardless of whether the number of elements in the sequence is 1, 2, 3, or 4 (Nieder et al., 2006). The tuning for preferred sequence position resembles that for preferred numerosity, in that different sets of neurons represent each of the possible ordinal positions. In fact, in VIP a larger proportion of neurons (∼22%) were selective for sequential quantity than were selective for simultaneous quantity (∼12%). The two populations did not overlap—that is—single neurons did not exhibit an abstract preference for "3," regardless of whether presented simultaneously or sequentially during the sample viewing period. During the delay period, when subjects are presumably holding an abstract representation of quantity in working memory, neurons representation of quantity did not depend on the format of presentation. Overall, the findings suggest coding for ordinal position as well as cardinal value in VIP that potentially drives representation of cardinal value in PFC.

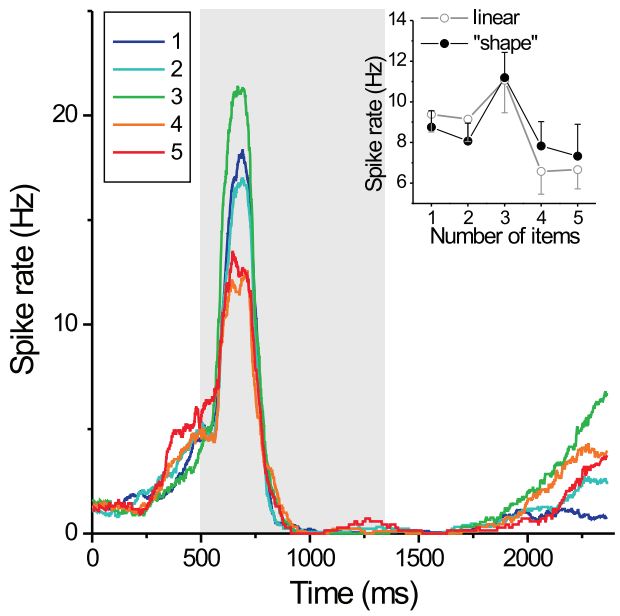

FIGURE 3 | Single neurons in posterior parietal cortex and prefrontal cortex (shown) respond most strongly for a "preferred" numerosity. In this example, firing rate was most elevated for arrays of "3" in a delayed-match-to-numerosity task, and declined with numerical distance from 3. Reprinted with permission from Nieder et al. (2002).

In the explicit delayed-match-to-numerosity task, it is possible that factors other than number modulated neural responses. The majority of number-selective neurons in PFC and PPC preferred the quantity "1" (Nieder et al., 2002; Nieder and Miller, 2004b). Behavioral studies also showed that monkeys' accuracy was highest when the sample value was 1 (Nieder and Miller, 2004a). An alternative explanation for the over-representation of the value 1 by neurons may be that the responses also convey information about reward expectations. It is possible that monkeys were more certain of achieving rewards when the sample value was 1, and this certainty is reflected in the discharge of some neurons categorized as preferring 1 (Leon and Shadlen, 1999). In this task, monkeys have extensive experience with a limited range of numerosities, and potentially treat cardinal number as other stimulus categories (Freedman et al., 2002; Freedman and Assad, 2006).

Extensive experience with categorization of visual stimuli as governed by task demands may contribute to the generation of different patterns of neural responses. In the non-symbolic numerical stimuli contain cardinal values of stimulus elements (e.g., 1, 2, 3, etc.), thus while we hypothesize that these values correspond to values drawn from a continuous representation of quantity, the stimuli themselves are inherently categorical. When monkeys were tasked with the discrimination of the continuous variable of line length, neurons in VIP exhibited tuning for one preferred line length from four possibilities, similar to tuning for cardinal value in numerosity tasks (Tudusciuc and Nieder, 2009). Thus, the delayed-match-to-sample task requires subjects to categorize even continuous stimulus characteristics, and the patterns of neural activity observed may be a product of experience and/or task demands. Indeed, when tested on comparisons of relative magnitude ("greater than" or "less than" a sample) PFC neurons did not show selective responses at the time the monkeys viewed the sample stimulus. Only when the monkeys were told which comparison rule to perform did task-related modulation emerge (Bongard and Nieder, 2010). Although monkeys viewed the same numerical arrays as those used in the delayed-match-to-numerosity task, the neural responses were qualitatively different. Rather than peaking for one cardinal value, most neurons represented the mathematical rule ("greater than," "less than"), suggesting that they carry higher-level cognitive signals, rather than performing a basic calculation of quantity. It is not known whether PPC neurons likewise might encode a rule for quantitative comparisons while monkeys perform this task, or if they maintain a representation of magnitude/cardinal value for such comparisons.

Given the human literature supporting a strong role for PPC in numerical cognition, it is perhaps surprising that a greater proportion of neurons in VIP and LIP were not driven by numerical stimuli in the previous studies. Several models of how to calculate numerosity from a set of elements include the process of accumulation as a critical step (Meck and Church, 1983; Dehaene and Changeux, 1993; Verguts and Fias, 2004). Neurons in LIP have

been proposed to integrate information with respect to their RFs. Monkeys discriminating the direction of motion of a random-dot stimulus behave as though they integrate the amount of information in the stimulus (measured as percent coherence) across the viewing duration (Gold and Shadlen, 2000, 2002). While monkeys view the motion stimulus outside of the RF, neurons in LIP show time- and motion coherence-dependent increases in activity that reach a common level when a decision to shift gaze into the RF is reached (Roitman and Shadlen, 2002). That is, when an eye movement is used to report the direction of visual motion, the activity of single LIP neurons increases with the amount of evidence favoring the eye movement toward its RF. Here, the integration of information is toward the initiation of a motor response. While related to the amount of information contained in the motion stimulus, the activity does not report the strength or direction of the motion in the manner of a sensory MT neuron (Britten et al., 1992). The pattern of activity exhibited by LIP neurons has been modeled as the accumulation of sensory information from visual area MT toward a "threshold," at which time a binary decision is complete and the eye movement initiated (Mazurek et al., 2003).

The notion that LIP neurons would estimate the number of stimuli within their spatially selective RFs by the computation of integration was directly tested using an implicit numerical discrimination task similar to that used to map numerical processing of the IPS in humans (Piazza et al., 2004). Here, monkeys passively viewed arrays of dots with different numerosities ranging from 2 to 32 located within the RF of each LIP neuron studied (Roitman et al., 2007b). In each block of trials, a standard numerosity (e.g., "8") was presented on half of the trials, while on the remaining half a deviant numerosity (2, 4, 16, or 32) was displayed. Although monkeys were required only to maintain fixation on a central point while the stimulus was displayed, presentation of a deviant stimulus predicted that the monkey would receive a larger reward for completing a gaze shift to a target in the opposite hemi-field from the RF when the fixation point was extinguished. Other stimulus variables (size, color, area, density) were controlled to not systematically vary with number.

When visual arrays were presented within the RFs of LIP neurons, and monkeys were not trained to explicitly discriminate numerosity, the majority of LIP neurons recorded (54%) had activity that was significantly modulated by the number of elements in the visual array. Neurons responded in a graded manner, either increasing or decreasing activity as the number of elements increased (**Figure 4**). Responses did not depend on other stimulus characteristics, or whether the numerosity served as standard or deviant in a given block of trials. The neurons with *increasing* responses resemble what would be expected by the integration of the number of elements within the RF. Similar monotonically increasing responses have also been observed in parietal neurons encoding the rate of a mechanical vibration applied to the fingertips (Hernandez et al., 2000, 2002). Neurons with responses that *decreased* with increasing numerosity may reflect the operation of other processes. In the random-dot motion discrimination, for example, LIP neurons show a time- and coherence-dependent reduction in activity when evidence favors a saccade away from the RF (Roitman and Shadlen, 2002; Mazurek et al., 2003). Multiple stimuli within a RF lead to competitive interactions and a reduction in activity in superior colliculus neurons, which are strongly interconnected with LIP (Li and Basso, 2005), in a process akin to divisive normalization (Carandini and Heeger, 2011).

Positive and negative profiles of graded responses are sufficient to support the basic characteristics of numerical judgments.

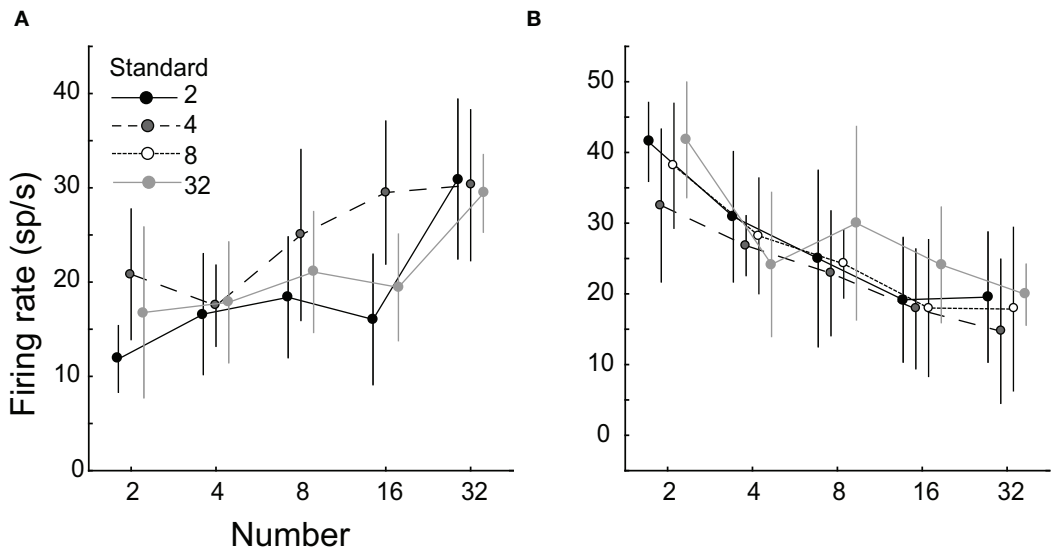

FIGURE 4 | Single neurons in the lateral parietal area (LIP) respond in a graded manner to numerosity. Arrays containing 4–32 elements were presented within the response fields of LIP neurons in an implicit task, while the subjects prepared to shift their gaze away from the array. Neuronal firing rate either increased **(A)** or decreased **(B)** with larger numerosities. From Roitman et al. (2007b).

In numerical bisection tasks, participants tend to treat the geometric mean of large and small anchor values as the subjective midpoint, e.g., 4 as the midpoint between 2 and 8 (Meck and Church, 1983; Jordan and Brannon, 2006). That the subjective midpoint falls at the geometric, rather than arithmetic, mean provides further evidence that mental estimations are based on ratio differences between numbers. Numerical bisection judgments also show superposition—regardless of the range of anchors tested (2 vs. 8, 3 vs. 12, 4 vs. 16) the probability that an intermediate value is judged as "large" depends its ratio to the "large" value. Bisection points at the geometric mean and superposing judgments can be predicted over a range of anchor values based on a calculation of the difference between the responses of positive and negative neurons reported in LIP (Pearson et al., 2010). Because the "ideal" performance of a pair of neurons with monotonic responses (one increasing and one decreasing) produce judgments with sensitivity greater than that exhibited behaviorally, the model matches behavior by pooling noisy neurons, much as that needed by computational comparisons of neuronal and psychophysical sensitivity in visual area MT (Shadlen et al., 1996). The graded response profiles of LIP neurons can, therefore, support numerical judgments consistent with Weber's law and without explicit representation of cardinal numerical value. This type of coding scheme of number has adaptive value as it can represent a wide range of values, without having to represent every possible number explicitly. To date, there are not data to address the maximum non-symbolic quantity that can be encoded with a graded coding scheme or the extent to which this value depends on experience/task-demands. For example, responses in LIP could increase to some maximum firing rate, which could correspond to the maximal numerosity the circuitry could represent. Alternatively, neural responses may adapt in order to encode multiple ranges of numerosities, such that when asked to discriminate values ranging from 1 to 5, the numerosity "5" elicits maximal responses, but when asked to discriminate values ranging from 2 to 64, scaling is compressed such that "64" elicits a maximal response, with less precision at intermediate values. The range over which such scaling might occur, and the adaptations single neurons might display have not yet been explicitly tested.

Thus, the measurements of single neuron responses to date yield two patterns of numerosity encoding-graded responses in LIP and peaked tuning curves for cardinal value in VIP and PFC. Models of numerical processing that ultimately represent cardinal number utilize an accumulation stage to sum the number of stimuli before converting this accumulated value to numerosity (Dehaene and Changeux, 1993; Verguts and Fias, 2004). These findings are consistent with models in which the representation of numerosity in VIP is derived from LIP inputs, and are then subsequently communicated to PFC to use as a categorical decision rule. Recent modeling has shown that units detecting the numerosity of visual stimuli emerge from a network learning to represent visual arrays (Stoianov and Zorzi, 2012). These numerosity detectors showed spatial selectivity like neurons in LIP, and encoded numerosity on a compressed analog scale. It is possible that differences in task demands and experience lead to the different patterns of responses in parietal cortex. In the implicit numerical discrimination task used by Roitman et al., monkeys were never required to employ the information about quantity to explicitly guide behavior. Behavioral data suggest that monkeys do attend to the numerosity of the stimulus, as saccade response times decreased with increasing differences of the deviant value from the standard, although there was no explicit report of cardinal value. In addition, stimuli in the implicit numerical discrimination task were tailored to the spatial properties of neurons, while those in the delayed-match-to-numerosity used by Nieder and colleagues were not.

The degree to which numerical sensitivity in parietal cortex depends on the spatial properties of the task performed remains unclear. Recent work has challenged the classical view of PPC physiological responses solely guiding sensorimotor transformations to guide spatial behavior. Neurons in LIP, originally thought to be involved in visual attention or oculomotor intention, have been shown to respond to stimuli outside of the RF. In monkeys reporting the category of the direction of a random-dot motion stimulus, LIP neurons also discriminated category identity, even when the stimuli were presented outside of the RF and the behavioral response was the (non-spatial) release of a lever (Freedman and Assad, 2009). Similarly, neurons in LIP report the decision about the direction of a random-dot motion stimulus (right vs. left) in the absence of an available choice target for motor planning (Bennur and Gold, 2011). This flexibility of PPC responses beyond the confines of spatially restricted RF is considerably greater than previously considered.

Behavioral evidence from human, infant, and animal studies suggest that numerosity is represented in a common, non-verbal format in which larger quantities are represented with less precision, resulting in judgments that follow Weber's law. Patients with PPC damage show deficits consistent with the notion that this region is necessary to support the estimation of quantity and understanding of the deep meaning of numbers. Converging findings from human imaging studies and non-human primate electrophysiological recordings support the idea that neurons within PPC respond to quantity with both graded responses that represent magnitude and tuning to identify cardinal value. While it has not been shown that the spatial arrangement of favors a more literal embodiment of a "number line," the physiological response profiles can functionally encode numerosity in a manner that can begin to account for the psychophysics of numerical judgments. Future investigations of the neural bases of numerical cognition should address a number of issues. Do these patterns of responses denote separate analog magnitude estimation and cardinal value systems? Is the representation of cardinal value derived from graded estimates of magnitude? To what extent are these representations innate, or do they depend on explicit training and experience? How do they form the basis for such simple computations as addition or division? The answers to these questions will undoubtedly shed light not only on the role of PPC in numerical cognition, but also its related abstract cognitive functions.

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Visual categorization and the parietal cortex

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The primate brain is adept at rapidly grouping items and events into functional classes, or categories, in order to recognize the significance of stimuli and guide behavior. Higher cognitive functions have traditionally been considered the domain of frontal areas. However, increasing evidence suggests that parietal cortex is also involved in categorical and associative processes. Previous work showed that the parietal cortex is highly involved in spatial processing, attention, and saccadic eye movement planning, and more recent studies have found decision-making signals in lateral intraparietal area (LIP). We recently found that a subdivision of parietal cortex, LIP, reflects learned categories for multiple types of visual stimuli. Additionally, a comparison of categorization signals in parietal and frontal areas found stronger and earlier categorization signals in parietal cortex arguing that, in trained animals, parietal abstract association or category signals are unlikely to arise via feedback from prefrontal cortex (PFC).

Keywords: neuroscience, categorization, learning, parietal cortex, LIP, frontal cortex, electrophysiology

INTRODUCTION

Parietal cortex was historically considered "association cortex" because it appeared to integrate sensory information to generate perceptions of the external world and guide body movements. Anatomical, physiological, and lesion data suggested that parietal cortex is well positioned to associate and adapt sensory information into a form that is useful for guiding behavior. Humans with lesions in the inferior parietal lobule do not experience basic sensory deficits, such as blindness or loss of somatosensation, but rather have more complex symptoms, including deficits in attention, movement planning, and spatial orientation (Critchley, 1953; Mountcastle et al., 1975).

Studies have pinpointed several brain areas that are involved in visual learning and categorization. Of these, lateral intraparietal area (LIP) is of particular interest, because it shares reciprocal connections with both early visual areas as well as higher cognition centers and is thus in an optimal position to integrate inputs from both regions. In this review, we focus on recent work in macaques which highlights LIP's role in categorization.

SPATIAL PROCESSING

Decades of work has elaborated robust modulation of parietal subdivision LIP by spatial attention and saccadic eye movements (Andersen and Buneo, 2002; Goldberg et al., 2006). Shadlen and colleagues have argued further that LIP encodes perceptual decisions in an "intentional framework" embedded within the motor-planning system (Shadlen et al., 2008). In these studies, subjects used saccadic eye movements to report their decisions, and signals related to decision and eye movements were observed in LIP. However, it is unclear how a decision system based on planning specific motor responses could be extended to explain more abstract decisions that do not necessarily result in specific and predictable motor responses (Freedman and Assad, 2011).

NON-SPATIAL PROCESSING

While most work on LIP has focused on its role in spatial processing, LIP neurons also show selectivity for various stimulus attributes during both passive-viewing and more complex behavioral paradigms. For example, LIP neurons respond selectively to the directions of moving random-dot stimuli (Fanini and Assad, 2009). LIP neurons also respond selectively to static, two-dimensional shape stimuli during passive viewing (Sereno and Maunsell, 1998; Janssen et al., 2008) and a delayed match-to-sample task (Sereno and Maunsell, 1998; Sereno and Amador, 2006). In these studies, stimuli were presented in neurons' receptive fields (RFs); thus the stimulus selectivity could not be explained by LIP spatial selectivity.

Visual-feature selectivity in LIP has been shown to change depending on the features that are relevant for solving a behavioral task. For example, LIP neurons are selective for color when colored cues are used to direct saccadic eye movements (Toth and Assad, 2002). In this study, monkeys were trained such that in alternating blocks of trials, either the color or location of a stimulus determined the direction of an upcoming saccade. When color was relevant, neurons were often color selective. In contrast, the same neurons showed much less color selectivity when cue location (but not color) was relevant for saccade planning. Moreover, when color was relevant for directing the saccade, the animal could not predict the upcoming saccade direction. Thus, color selectivity was not an artifact of saccade planning or spatial selectivity. This suggests that LIP can encode arbitrary stimulus

properties not simply when they are important for guiding an action, but also when they are relevant to solving a task.

Posterior parietal (including LIP and 7a) neurons may also encode the "rules" that dictate how the animals should link stimuli to responses. Stoet and Synder trained monkeys on a task-switching paradigm in which the animals alternated between two stimulus-response mappings (Stoet and Snyder, 2004). A pre-trial task cue instructed animals to discriminate either the color or orientation of a subsequent test stimulus to generate an appropriate response. Neurons in areas of posterior parietal cortex, including LIP, were selective for the task rules even before the test stimuli were turned on. These studies show that LIP activity reflects cognitive signals that are not related to spatial encoding; moreover, they suggest that LIP activity reflects changes in behavioral demands.

CATEGORICAL ENCODING

These experiments showed that LIP is involved in functions beyond spatial processing and raise the possibility that LIP plays a general role in cognitive processing. A strong test for the presence of abstract cognitive signals is whether LIP neurons represent categories. Categorization is a fundamental cognitive ability that assigns meaning to stimuli. Stimuli in the same category may be physically dissimilar, while stimuli in different categories may be physically similar. For instance, a wheel and a clock may look alike, but serve different functions. Categorical signals have been observed in prefrontal cortex (PFC) when monkeys learned to categorize morphed visual stimuli as "cats" or "dogs" (Freedman et al., 2001). In contrast, neurons in inferior temporal (IT) cortex showed very weak category encoding, but were strongly selective for the features of visual stimuli (Freedman et al., 2003).

Freedman and Assad (2006) asked whether direction selectivity in LIP is plastic depending on the category rule used to solve the task. Two monkeys performed a delayed-match-to-category task, in which they learned to group 360° of motion directions into two 180°-wide categories. The stimuli were patches of high-coherence random-dot movies. Animals were presented with a sample and a test stimulus separated by a delay period. If the sample and test directions belonged to the same category, animals released a touch-bar to receive a reward. Because the sample and test categories were chosen randomly on each trial, animals could not predict during the sample and delay periods whether to release or to continue holding the touch-bar to a future test stimulus.

After the animals were proficient in the direction categorization task, LIP activity was recorded during task performance. Sample and test stimuli were placed in neurons' RFs in order to elicit strong visual responses. Neuronal activity reflected the learned motion categories—that is, individual neurons tended to show smaller differences in firing rate *within* categories, and larger differences in firing rate *between* categories. This effect was present during stimulus presentation and the subsequent delay period, when no stimulus was present in the RF. The animals were then retrained on a new category boundary over the course of several weeks, and a second population of neurons was recorded. After the monkeys learned the second boundary, LIP selectivity had "shifted" dramatically away from the previous category boundary and reflected the new category boundary. Thus, LIP activity changes to reflect the learned category membership of visual stimuli. Similarly, PFC neurons showed similar shifting of representations following retraining (Freedman et al., 2001) and differential activity when identical stimuli are classified according to varying rules (Roy et al., 2010).

In contrast, neurons in the middle temporal area (MT), which is directly interconnected with LIP, were little affected by category training. MT contains a preponderance of neurons that are selective for motion direction (Born and Bradley, 2005), and nearly all of the recorded MT neurons were also highly direction selective in the direction categorization task. The preferred directions of individual MT neurons were distributed almost uniformly in the direction categorization task and thus did not reflect the category boundary or category membership of the motion stimuli (Freedman and Assad, 2006). Because motion category selectivity was absent in area MT but present in LIP, an intriguing possibility is that directional signals in MT are transformed into more abstract categorical representations in LIP. This could occur via plasticity within the hierarchy of parietal cortical processing or even in the direct interconnections between MT and LIP.

Freedman and Assad examined how LIP's categorical signals interact with spatial signals by varying the position of the direction stimuli with respect to the RF of the neuron under study (Freedman and Assad, 2009). Not surprisingly, LIP neurons were strongly modulated according to whether stimuli were presented within or outside their RFs—nearly all LIP neurons showed much lower activity when the stimuli fell outside of their RFs; however, many LIP neurons still showed modulation by the direction categories despite their weak firing rates, suggesting that LIP categorization signals are orthogonal to spatial signals. Open questions include how spatial signals in LIP (e.g., signals related to attention or eye movements) are multiplexed with non-spatial signals, and how both spatial and non-spatial signals are "read out" from LIP by downstream brain areas.

ENCODING OF LEARNED SHAPE-SHAPE ASSOCIATIONS

LIP activity flexibly changes with the demands of a direction categorization task, but does this flexibility extend to other visual stimuli? Selectivity for learned direction categories may be a special case, because the continuous, native parametric tuning for direction in parietal neurons may provide a "scaffold" upon which the categorization signals emerge (Ferrera and Grinband, 2006). In fact, visual-motion patterns were chosen for that study because LIP neurons were known to respond to such stimuli. Alternatively, LIP may reflect learned associations between other visual stimulus attributes besides direction. This would suggest that LIP plays a more general role in encoding learned associations between visual stimuli, much like that ascribed to frontal cortical areas such as the lateral PFC (Miller et al., 2002; Cromer et al., 2010). Since LIP has been shown to respond selectively to non-spatial visual stimuli, such as color (Toth and Assad, 2002) and shape (Sereno and Maunsell, 1998), LIP may also encode associations between such diverse stimulus features.

To examine the generality of learned associations in parietal cortex, Fitzgerald and colleagues asked whether LIP neurons reflect arbitrary associations between pairs of visual shapes (Fitzgerald et al., 2011). Animals learned to associate pairs of static, two-dimensional shape stimuli in a delayed pair association task. The shapes were paired arbitrarily, and different pairing schemes were used for the two animals in the study. Finding shape pair selectivity in LIP would provide evidence that associative representations are a general property of LIP neurons, and are not specific to particular stimulus attributes such as direction.

Pair-association learning tasks have been used extensively to study neurons in the ventral visual stream, particularly by Miyashita and colleagues. For example, Sakai and Miyashita described IT neurons that are activated specifically by one pair of shapes, which had been associated with one another over the course of long-term training, during the sample and/or delay intervals of a delayed pair association task (Sakai and Miyashita, 1991). Further work described pair-association effects in perirhinal cortex (Naya et al., 2003), hippocampus (Wirth et al., 2003; Yanike et al., 2004), PFC (Rainer et al., 1999), and there is some evidence for associative effects in MT (Schlack and Albright, 2007).

After monkeys were well-trained on the shape pair associations, Fitzgerald et al. (2011) recorded from LIP as animals performed the task. A majority of LIP neurons reflected the learned shape-shape associations, such that the neurons showed more similar activity for shapes that had been associated with one another and distinct activity for the non-associated shapes (**Figure 1A**). These results provide evidence that LIP neurons can encode associations for broad classes of visual stimuli and that LIP may play a general role in forming visual associations. Whether associative signals in LIP might be observed for stimuli from other sensory modalities (e.g., audition or somatosensation) remains unknown.

ENCODING OF ASSOCIATIONS FOR MULTIPLE TYPES OF VISUAL STIMULI

While LIP activity can reflect learned associations between shapes as well as motion categories, a second question is whether *individual* LIP neurons encode associations for *both* shapes and motion, or rather only encode associations for particular classes of visual stimuli. The question is germane because LIP receives broad inputs from other visual cortical areas (Blatt et al., 1990; Lewis and van Essen, 2000), and inputs from the dorsal and ventral visual streams—which are considered specialized for spatial and object processing, respectively (Mishkin et al., 1983)—are anatomically segregated along the dorsal-ventral axis of LIP (Lewis and van Essen, 2000). The segregated pattern of visual input to LIP might suggest that individual LIP neurons are specialized for forming associations for either shapes or directions, but not both. Such specialization would suggest that LIP's involvement in categorization is limited, and that the information represented in LIP alone is not sufficient for solving abstract categorization tasks. If instead individual LIP neurons can form associations for *both* stimulus types, this would reinforce the notion that LIP neurons are capable of forming broad

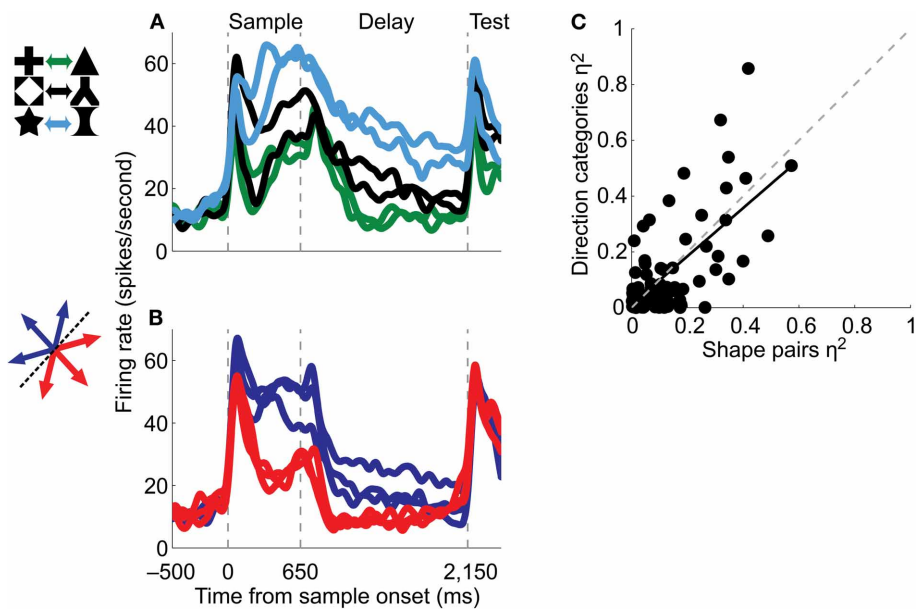

FIGURE 1 | Single neurons reflect both shape-shape associations and motion direction categories [Fitzgerald et al. (2011)]. **(A)** The activity of a single LIP neuron as a monkey associated six shapes into three pairs in a delayed-match-to-pair task. The average neuronal activity evoked by each sample shape is plotted, and same-color traces correspond to associated pairs of shapes. **(B)** The same neuron was recorded while the animal performed a delayed-match-to-category task. Average activity evoked by each sample motion direction is shown, and same-color traces correspond to directions in the same category. **(C)** Association or category strength, as measured by explained variance (η^2) for direction categories versus shape pairs, during the first half of the delay period for all neurons tested in both tasks. The solid line is a regression fit, and the dashed line has a slope of 1.

associations for a wide range of visual stimuli. This might suggest that LIP can encode the outcome of any task in which the animal must arrive at a discrete outcome or decision—e.g., "category one" versus "category two" or "pair A" versus "pair C" (Freedman and Assad, 2011). This would be particularly interesting because it would potentially link associative or categorical representations in LIP with discrete decision-related activity in LIP that has been described by Shadlen and colleagues (Gold and Shadlen, 2007).

To examine the generality of associative representations in LIP, monkeys were trained to alternate between blocks of the shape and direction categorization tasks. LIP neurons that were selective for the shape pair associations also tended to be selective for the direction categories (**Figures 1A,B**), and there was a positive correlation between the strength of associative encoding in the two tasks (**Figure 1C**). This argues that single LIP neurons may generally encode associations between any types of visual stimuli and supports the hypothesis that LIP neurons are modulated whenever animals must determine a discrete outcome or decision. This hypothesis is supported by a study that dissociated perceptual decisions from the direction of the saccades used to signal the decisions and found that decision signals were encoded independently of the eye-movement (Bennur and Gold, 2011). Thus, LIP may generally encode categorical decisions and associations independently of spatial or motor planning.

CATEGORIZATION SIGNALS IN LIP COMPARED TO PFC

PFC neurons have been shown to reflect the category membership of visual shapes for one (Freedman et al., 2001) or two categorization rules (Cromer et al., 2010; Roy et al., 2010). However, the relationship between category signals in PFC and LIP had been unclear, as the two areas had not been directly compared. One possibility is that visual categories are computed in PFC, which is often considered the executive, decision-making center of the brain, and then sent to LIP via top-down connections. To directly assess the roles of these two areas, Swaminathan and Freedman (2012) recorded from single neurons in LIP and PFC during the motion direction categorization task. In this experiment, LIP showed stronger and more reliable category encoding than PFC. Moreover, category signals appeared with a shorter latency in LIP than in PFC (**Figure 2**), and LIP's stronger categorization signals were robust even after adjusting for differences in the strength of firing rate and category selectivity between the two brain areas. This finding argues that categorical signals in LIP during this task are unlikely to be driven by PFC, and raises the possibility that LIP or another brain area may be a source for category signals observed in PFC.

The finding that PFC showed weaker and longer latency category signals than LIP during the direction categorization task (Swaminathan and Freedman, 2012) places important constraints on the neural circuitry underlying the categorization process. An appealing hypothesis that arises from the comparison of MT, LIP, and PFC is that motion direction encoding in MT may be transformed into category encoding in LIP via learning-dependent changes in the direct synaptic connections between the two areas. However, a key consideration is that the direct cortical-cortical connection between MT and LIP is only one pathway by which information can propagate between these two areas. For example, MT and LIP are both interconnected with motion-sensitive regions such as the medial superior temporal (MST) and ventral intraparietal (VIP) areas (Lewis and van Essen, 2000). LIP and PFC are also interconnected with parietal area 7a, in which several recent studies have found category-related neuronal signals (Merchant et al., 2011; Goodwin et al., 2012) and the medial intraparietal area. While anatomical studies have demonstrated the interconnections between these areas, their relative positions in the information processing hierarchy are poorly understood. Categorical signals have also been observed in the frontal eye fields (Ferrera et al., 2009), and a network of other regions, including sensory cortex, motor cortex, the medial temporal lobe, and basal ganglia (Seger and Miller, 2010).

DEVELOPMENT OF CATEGORY SIGNALS DURING LEARNING

In the categorization studies described above, neuronal activity was examined only after the monkeys were fully trained on the categorization or pair association tasks. Because of this, much less

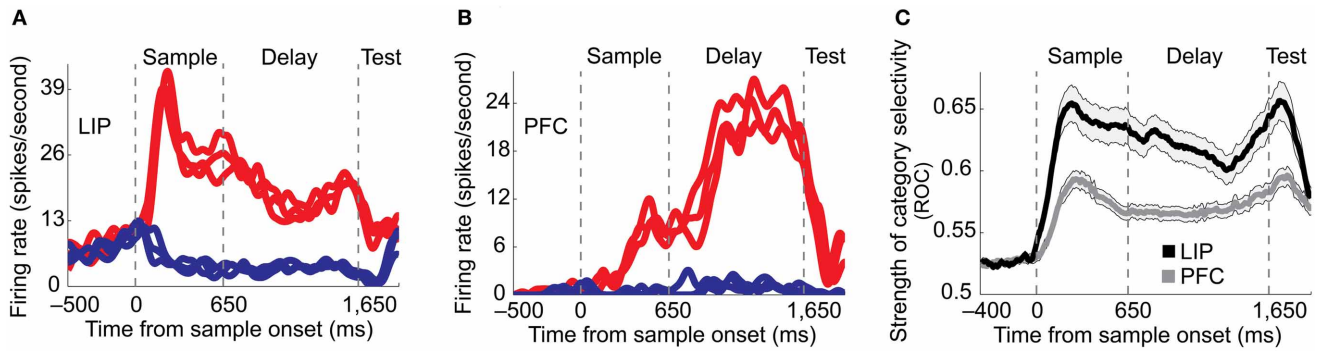

FIGURE 2 | Comparison of LIP and PFC in a motion direction categorization task [Swaminathan and Freedman (2012)]. **(A–B)** Examples of category-selective neurons in LIP **(A)** and PFC **(B)**. Single neurons in both areas displayed binary-like category selectivity during the motion direction categorization task. Same-color traces correspond to directions in the same category. **(C)** Category selectivity, measured by receiver operating characteristic (ROC) analysis was stronger and appeared with a shorter latency in LIP (black) compared to PFC (dark gray). The shaded area around the solid traces indicates the s.e.m.

is known about the roles of LIP and PFC during the learning process itself. While LIP showed more reliable and shorter latency category effects than PFC after the learning process was complete, PFC might be more involved in the initial category-learning process. Strong category signals might not emerge in LIP until late in the learning process, once the categories are highly familiar. Alternatively, LIP might be more directly involved than PFC during the category-learning process as well as after learning is complete. This is supported by the finding that LIP neurons reflect dynamic stimulus-response mappings (Toth and Assad, 2002) and dynamically changing task rules (Stoet and Snyder, 2004). Further, LIP showed a stronger coupling than PFC with the monkey's trial-by-trial classifications of ambiguous stimuli (Swaminathan and Freedman, 2012). A key question for future work is to examine the role of parietal cortex in the category learning process, particularly in comparison with PFC, in which category representations have been shown to arise in parallel with the learning process (Antzoulatos and Miller, 2011). If category selectivity appears with a shorter latency in PFC than LIP during category learning, this would suggest that PFC may have a critical role in category learning, and LIP only becomes involved when subjects are experts at the task. Alternatively, if LIP showed category encoding earlier than PFC during learning, it would indicate that LIP is also strongly involved in the category learning process.

SUMMARY

Together, the studies described here represent progress toward understanding the neuronal mechanisms underlying the learning and recognition of visual associations and categories. The brain-wide circuit underlying categorization processes is likely to include a large network of brain areas. However, recent work suggests that the parietal cortex and LIP in particular, is more involved in encoding abstract associative and categorical factors than its traditionally ascribed role in visual-spatial processing might suggest.

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Neural correlates and neural computations in posterior parietal cortex during perceptual decision-making

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A recent line of work has found remarkable success in relating perceptual decision-making and the spiking activity in the macaque lateral intraparietal area (LIP). In this review, we focus on questions about the neural *computations* in LIP that are not answered by demonstrations of neural *correlates* of psychological processes. We highlight three areas of limitations in our current understanding of the precise neural computations that might underlie neural correlates of decisions: (1) *empirical questions* not yet answered by existing data; (2) *implementation issues* related to how neural circuits could actually implement the mechanisms suggested by both extracellular neurophysiology and psychophysics; and (3) *ecological constraints* related to the use of well-controlled laboratory tasks and whether they provide an accurate window on sensorimotor computation. These issues motivate the adoption of a more general "encoding-decoding framework" that will be fruitful for more detailed contemplation of how neural computations in LIP relate to the formation of perceptual decisions.

Keywords: LIP, posterior parietal cortex, decision-making, neurophysiology, neural correlates

INTRODUCTION

> *"It is an hypothesis that the sun will rise tomorrow: and this means that we do not know whether it will rise."*
>
> —L. Wittgenstein

Some tests of hypotheses are more exciting than others. When measuring neural signals in the lateral intraparietal cortex (LIP) of monkeys while they perform decision-making tasks, it is no longer particularly exciting to observe a correlation between the aggregate spike rate in LIP and the formation of decisions over time. This attitude reflects remarkable recent progress: over the last decade and a half, there have been a large number of demonstrations of LIP activity mirroring the inferred processes of accumulating evidence for the purposes of making a decision during performance of a moving-dot direction discrimination task (reviewed below; also see Gold and Shadlen, 2007).

In this article, we focus on the moving dots paradigm as a specific arena for exploring what such demonstrations of neural correlates tell us about LIP, in part because of our personal familiarity with the details, and in part because the level of detail in this body of work makes for a particularly fruitful discussion. However, this discussion aims for traction with readers who are not yet experts in the dots task paradigm, so we begin by briefly summarizing some of the key results and describing the neural correlate framework. We attempt not just to celebrate the successes of this approach, but to focus scrutiny on what we have not yet learned about LIP function from it. We argue that we know very little about what LIP responses are driven by, how LIP neurons transform their signals into outputs, and what these outputs mean. We propose that this arises from a growing emphasis on neural correlates of psychological processes, over a focus on neural computations of the sort that guides most work in sensory and motor systems. In short, the observation of a neural correlate does not necessarily reveal neural computations. Our goal here is to highlight this distinction, and then attempt to lay groundwork for an increased emphasis on neural computations in posterior parietal cortex.

We conclude that using a more general "encoding-decoding framework" will aid us in unpacking the neural computations in LIP during perceptual decision-making. This framework, which has already proven successful in the study of sensory and motor function, has perhaps even greater potential for unpacking many mechanistic questions about how LIP comes to represent neural correlates of decision variables. Success in this endeavor would also support a more detailed integration of results across the broader literature on LIP function, which contains a variety of experimental paradigms focused on attention, motor intention, visual search, reward expectation, and/or categorization (e.g., Gnadt and Andersen, 1988; Platt and Glimcher, 1999; Bisley and Goldberg, 2003; Dorris and Glimcher, 2004; Sugrue et al., 2004; Freedman and Assad, 2006; Ipata et al., 2006; Thomas and Paré, 2007).

BASIC LIP RESPONSES

The longstanding approach for characterizing the basic sensorimotor properties of LIP neurons starts with a simple, instructed eye movement task. When a saccade target is presented in the response field (RF) on an LIP neuron, it usually elicits a brisk visual response. When the subject (a trained rhesus monkey)

eventually makes a saccade to that target, the eye movement is complemented by a response burst as well. Thus, the same neuron can exhibit both sensory and (oculo-) motor responses. Furthermore, many LIP neurons also show a persistent, elevated firing rate across the temporal delay between these two events—even when the saccade target is only flashed quickly, and the monkey is required to wait many hundreds of milliseconds before making a saccade to the remembered target location (Gnadt and Andersen, 1988). This persistent activity looks like an explicit neural correlate of the working memory process required in this simple sensorimotor task.

Because the persistent activity of these neurons appeared to explicitly bridge the temporal gap between sensory input and motor output, such cells were theorized to be windows into simple forms of higher cognition (Shadlen and Gold, 2004). Persistent activity allows a neuron's response to be temporally dissociated from the immediate time scales of sensory and motor events, which is likely a key element in the generation of well-considered and temporally-appropriate behaviors in response to prior events (Mountcastle et al., 1975; Fuster, 1997). Furthermore, LIP activity is less tightly related to the occurrence and metrics of saccades, especially compared to related oculomotor areas (Shibutani et al., 1984). Given these putatively "cognitive" response characteristics, LIP is often targeted in neurophysiological investigations of simple cognitive tasks. Although many interesting tasks have been used to probe LIP, here we focus on a particular paradigm that has focused on relating LIP activity to the formation of decisions. This emphasis allows us to discuss detailed neural correlates and neural computations, but the points to be drawn from this exercise are hopefully more general.

THE BASIC "DOTS TASK"

A moving-dot direction-discrimination task (hereafter called the "dots task") (e.g., Newsome and Paré, 1988) has been frequently used to investigate decision-related signals in area LIP. In this task, the experimental subject performs forced-choice direction discrimination on a random dot kinetogram of variable signal strength. Coherent motion is generated by displacing some proportion of the dots with a spatiotemporal step that yields visual motion. The remainders of the dots are simply replotted in random locations and serve as noise, resembling analog TV snow. The fraction of signal dots is called the "motion coherence," and serves as a simple way to manipulate the signal-to-noise ratio of motion. The resulting motion is very obvious if the coherence is high or very subtle if the coherence is low. A zero coherence stimulus, which is not readily discernible from a low nonzero coherence stimulus, serves as an elegant means for relating neural to behavioral variability on a single trial level (Parker and Newsome, 1998).

The moving dot stimulus has many important psychophysical properties. First, it yields well-behaved psychometric functions, with a gradual transition from chance to perfect accuracy as coherence is increased. It should also be noted that the signal dots (those chosen to move coherently) are selected anew at random from video update to update. This means that any particular dot is unlikely to continue along a coherent-motion trajectory for a significant amount of time; a signal dot at one point is likely to become a noise dot later, and vice versa. This stochastic nature of the stimulus is likely advantageous: it requires subjects to broadly integrate the net motion over space instead of trying to track a single signal dot; also, it contains a degree of "spatiotemporal splatter" that invites subjects to integrate the directional signals over time. A relatively long psychophysical temporal integration period allows neurophysiologists a longer time period to consider neural responses during a gradual formation of decisions.

This type of random dot kinetogram was originally used by psychologists as a careful stimulus for studying the perception of visual motion (e.g., Anstis, 1970), but the psychophysical components of the dots task proved critical for seminal studies that investigated the relation between the neural activity of middle temporal visual area (MT) and perceptual decisions (e.g., Newsome et al., 1989; Britten et al., 1992). The dots task then evolved into a well-controlled experimental paradigm for studying LIP signals while monkeys decided which direction of motion was presented, and communicated their choice with an eye movement to one of two choice targets located inside and outside of the LIP neuron's RF (Shadlen and Newsome, 1996). Just as the early investigations of LIP focused on visually-instructed saccades to the RF, these later studies focused on visually-informed decisions to make a saccade either to the RF or to another location.

Use of the dots task for studying decision signals in LIP was enriched by the fact that the earlier studies using the same paradigm had quantitatively characterized the responses of MT neurons to these stimuli (Newsome et al., 1989; Britten et al., 1992, 1993), and had also compellingly demonstrated that these MT signals were used by the monkeys in performing the task (Newsome and Paré, 1988; Britten et al., 1996). In short, MT neurons of course exhibited direction-selective responses to the moving dot stimuli. But they also exhibited a remarkably simple dependence on the coherence of the motion: For a preferred direction of motion, MT responses increased linearly with increasing coherence; for anti-preferred direction motion, MT responses decreased linearly with coherence, although this decrease was quantitatively shallower than the increase associated with preferred directions. Furthermore, the temporal pattern of MT responses was relatively simple; after a fixed response latency and a brief onset transient, MT neurons responded briskly during stimulus presentation, exhibiting a generally flat firing rate throughout. Additional quantitative measurements yielded precise characterizations of the signal to noise of these sensory responses (Britten et al., 1993).

Recording from LIP during the dots task reflected an opportunity to observe the transformation of the precisely-characterized sensory signals in MT into a decision to move the eyes in LIP. Given that MT signals appeared to be relatively faithful and simple representations of the sensory stimulus, LIP responses had the potential to be approached as performing a computation upon the directional "evidence" coming from MT (Shadlen and Newsome, 2001). This relationship was supported by anatomical projections from the MT complex to LIP (Lewis and Van Essen, 2000a,b), as well latencies of direction- and coherence- dependent responses in LIP lagging those in MT during the dots task (Mazurek et al., 2003).

Single-unit recordings in LIP during the dots task revealed a pattern of response that still depended on motion direction and coherence, but that showed temporal dynamics substantially different from the simple MT responses. Instead of firing at a nearly constant rate that could be conceived of as an instantaneous representation of the sensory stimulus, LIP responses ramped upwards or downwards while the monkey discriminated the direction of motion (Shadlen and Newsome, 1996). It is this ramping of the LIP response during decision formation that has been interpreted as a neural correlate of the gradual accumulation of evidence during direction discrimination, for the purpose of ultimately making a saccade either into or out of the neuron's RF.

More precisely, the LIP spike rate would ramp up (or down) before an eventual saccade into (or out of) the RF, with a slope that depended systematically on the motion coherence. Higher coherences led to steeper ramps; lower coherences led to shallower ramps. It was as if the LIP firing rate was a direct neural instantiation of the accumulation of evidence (Shadlen and Newsome, 1996). Later in the trials, after the discrimination part of the trial was over, the neural response reached a common level immediately before a saccade into the RF. If the ramping responses during the moving dot stimulus reflected the accumulation of evidence, then the constant pre-saccadic level might be interpreted as a neural correlate of the results of that deliberation—perhaps a high or low state corresponding to the decision itself.

These initial interpretations of LIP activity were bolstered by later work that more rigorously focused on the decision-making phase of each trial. The initial LIP studies employed relatively long viewing durations and subsequent delay periods that were under the experimenter's control. Although this allowed the experimenters to distinguish the stimulus and the behavioral response by separating them in time, it was unclear exactly when the monkey made his or her decision. In fact, it was not just possible, but probable, that the direction discrimination task might be completed on most trials well before the stimulus was extinguished (Kiani et al., 2008). Later psychophysical results in both monkeys and humans confirmed this, suggesting that high coherence decisions were likely completed almost instantaneously (on order of 100 ms) but that lower coherence decisions reflected several hundreds of milliseconds of deliberation (Gold and Shadlen, 2003; Palmer et al., 2005).

In a critical neurophysiological study (Roitman and Shadlen, 2002), monkeys were trained to perform a response-time version of the dots task, in which they were allowed to make a saccade as soon as they desired. After training, the monkeys performed the task by indeed taking longer for lower coherences. Thus, just as their discrimination accuracy exhibited a systematic increase with coherence, their response times followed a systematic decrease along the same axis. During this version of the task, LIP responses ramped over approximately the same amounts of time that the monkeys were likely continuing to accumulate evidence. The LIP response at the time of the saccade was also striking: the coherence-dependent ramps converged within a few tens of milliseconds before the actual saccade. This was all the more consistent with the original supposition that LIP firing rates reflected not just the accumulation of evidence but also the end result of the decision process (of course, by allowing the saccade and the decision to ostensibly co-occur under the monkey's control, the interpretation of the neurophysiology requires additional care).

DRIFT DIFFUSION FRAMEWORK

The interpretation of coherence-dependent ramping of LIP responses as a neural correlate of the accumulation of evidence is not merely qualitative. In fact, LIP responses during the dots task are tempting to relate to a significant theory from mathematical psychology known as the drift-diffusion model. Originally posited by Ratcliff (1978)— and successfully applied to fit many findings in cognitive psychology (e.g., Ratcliff and Rouder, 1998, 2000; Ratcliff et al., 1999; Ratcliff, 2002)— the drift-diffusion model is derived from a quantitative analogy between the psychological accumulation of evidence to a decision bound, and the physical diffusion of a particle in the presence of absorbing boundaries. In the context of a perceptual discrimination task, the drift rate of this diffusion process can be controlled by the stimulus, in which stronger stimuli lead to more pronounced drift rates toward the corresponding bound. However, the process is noisy, so in the presence of weakly or moderately biased drift, there is variability both in which bound is hit, and the precise time at which it arrives.

The diffusion model thus makes predictions for the accuracy and speed of decisions using a single elegant mechanism whose heart is temporal integration. By conceiving of the process of accumulation as a noisy random walk of a decision variable toward one or another bound, a simple two-alternative task (like the dots task) could adopt the mathematical underpinnings developed by physicists to model diffusion processes. Although it required formidable insight to establish this conceptual relation, and considerable ingenuity to implement it, the psychological theories were ultimately able to rely on convenient mathematical expressions of bound-passing times that predict the speed and accuracy of decisions.

Despite the widespread application of this model to a variety of memory and decision-making tasks, its neurophysiological implementation did not receive much focus until recently (Ratcliff et al., 2003). Although there are certainly differences of opinion across the field, many cognitive psychologists likely remained agnostic about the underlying neural mechanisms. Just because a mathematical model based on noisy random walks often accounted for the pattern of reaction times, there was no consensus among researchers that the brain directly implemented such a process (although there was already remarkable progress relating neurophysiology to accumulator models of decision-making; see Hanes and Schall, 1996).

It was therefore rather striking how much LIP responses resembled the hypothetical processes in the drift-diffusion model over several hundreds of milliseconds. With the reasonable assumption that drift rate is a function of motion coherence, the well-known plots showing average LIP response as a function of time and coherence look a lot like the biased random walks of the drift-diffusion model. Furthermore, a very simple form of the drift-diffusion model does an excellent job of accounting for behavioral accuracy and response time in the moving dots task (Palmer et al., 2005). A simulation of LIP responses confirmed

that they are well-approximated by an underlying temporal integration of noisy sensory signals from area MT (Mazurek et al., 2003), although a more realistic model using real LIP responses has yet to be undertaken (but see Purcell et al. (2010) for a successful implementation of this approach in the frontal eye fields).

To summarize, LIP responses during the dots task resemble the variables posited by the drift-diffusion model, and the drift-diffusion model accounts for psychophysical performance in the same task. This led many to adopt a framework in which LIP activity was a direct neural instantiation of the decision-making process described by drift-diffusion, i.e., that the accumulation of evidence as described by drift-diffusion was explicitly represented in the spike counts of single neurons in LIP. Because drift-diffusion has a clear mathematical implementation, the fidelity with which LIP matched this process makes it a particularly appealing quantitative form of a "neural correlate." In the following section, we review some extensions of this work that further generalized this quantitative link and made the correlation between LIP and a diffusion process even more striking.

EXTENSIONS OF THE DOTS TASK

This basic link between LIP response and a theoretical decision variable has been aggressively explored and extended over the last decade or so. For example, Churchland and colleagues (2008) included a condition with four choice targets (and four potential coherent motion directions) instead of the conventional two. They observed many of the same aspects of LIP responses described above (e.g., coherence-dependent ramping), but also observed a lower initial firing rate in the four-choice trials. This was interpreted as a lower starting point for evidence accumulation, which is intuitive, because with more alternatives the decision will likely require more deliberation. A 3-alternative version of the dots task has also received psychophysical and modeling attention (Niwa and Ditterich, 2008; Ditterich, 2010). Furthermore, similar effects of the number of choice alternatives have been observed in other tasks in LIP (Louie et al., 2011) and other oculomotor areas (Basso and Wurtz, 1998; Lee and Keller, 2008).

In another ambitious extension, the dots task was modified to contain a third target option, presented at end of moving dot stimulus that constituted a "sure thing"— a small but certain reward (Kiani and Shadlen, 2009). On trials in which the monkey eventually chose this smaller but certain stimulus, the LIP response during the dots was muted. If LIP responses reflect the accumulation of evidence, a slightly lower level would suggest trials in which evidence was not acquired as quickly as usual. This lower level of accumulated evidence could in turn correspond to a lower confidence, and hence the selection of the "sure thing" target on those choices.

Another interesting task variant generalized the dots task to less certain mappings between motion direction and saccade generation (Bennur and Gold, 2011). In this version, the two choice targets were colored differently, and the monkeys learned that a particular direction of motion corresponded to choosing a particular *color* target (as opposed to the usual spatial selection of a target in a particular location that is consistent with the direction of motion). Critically, the differential target colors were revealed either at either an early, middle, or late period of the task. Although there are many nuances in the results of this study, the core result was that the conventional decision-related signals emerged in LIP when the choice targets (and hence the direction of the saccade) were disambiguated. That said, some neurons showed decision-related activity before that disambiguation, although of course the mapping between saccade direction and this activity was idiosyncratic. The interpretation, couched in the context of the drift-diffusion model, is that these latter LIP neurons perform a more general, and response-independent accumulation of evidence (Fanini and Assad, 2009), complementing the more conventional sensorimotor mapping seen in the usual version of the task.

Finally, a trio of recent studies has explored how other decision-related factors are reflected in LIP during the performance of the dots task. One study (Rorie et al., 2010) manipulated the reward associated with different directions of motion, and observed that LIP responses were higher for the direction with the larger reward. Because this reward effect was present from early in the trial, and was roughly additive in nature, these physiological observations can be interpreted as the reward affecting the starting point of the evidence accumulation, without much affecting the rate of the accumulation of evidence. Another study (Hanks et al., 2011) manipulated the relative prior probabilities of the two directions of motion, and found that LIP spike rates were larger for the more likely direction, but that the magnitude of this increase depended on stimulus reliability (and/or elapsed time). These observations lead the investigators to posit a novel modification to the drift diffusion model, where elapsed time is used to determine how much weight to apply to sensory evidence relative to prior probabilities. In contrast to those findings, another study manipulated prior probabilities (Rao et al., 2012) but found a largely additive effect on LIP responses instead. Such a modulation can of course be interpreted in terms of an additive offset of the accumulation of evidence, although it differs from the dynamic bias signal observed by Hanks and colleagues. The reason for these different effects of bias may be due to experimental differences (i.e., the latter study used an explicit visual cue to signal changes in prior probabilities from trial to trial), but the only definitive point that can be made is that both types of effects could be interpreted in terms of simple effects on a drift diffusion process. Other studies using different oculomotor choice paradigms have also observed strong modulations of LIP response for these non-sensory components of decisions (e.g., Platt and Glimcher, 1999).

These examples suggest that the link between LIP and the drift diffusion model is robust and general. In these novel variants and extensions of the task, LIP responses can still be interpreted as directly mapping on to the accumulation of evidence over time, up to (or near) the point of making a decision. The goal of the following sections, however, is to contemplate phenomena and levels of analysis that fall outside of this neural correlate framework in the hopes of gleaning additional insight into LIP's function.

EMPIRICAL QUESTIONS

The similarity between LIP responses during the dots task and the accumulation of evidence modeled by the drift-diffusion framework is certainly appealing. It reveals a quantitative, parametric

relation between spike rates in LIP and an inferred decision variable, across multiple variants of the dots task. However, looking beyond these successes reveals a number of empirical questions (still accessible within the dots task) that are yet to be systematically investigated. When acknowledging the richness of sensorimotor responses in LIP, it is not surprising that there are many nuances of response that might provide leverage into the computations performed in this area.

Although it seems trivial (and less interesting) compared to LIP's ramping response, the largest response seen in many LIP neurons is elicited simply by the appearance of choice targets at the start of the trial. The onset of the choice target within the RF can create a quick and robust response, as can also be seen in simpler instructed-saccade tasks (Bisley et al., 2004). In the context of the dots task, this strong transient response is typically considered irrelevant because it occurs well before the onset of the moving dots and the decision phase of the trial. This response is sometimes not evident in published peri-stimulus time histograms that align the responses to the onset of the moving dots (e.g., Shadlen and Newsome, 2001; Huk and Shadlen, 2005, but see Churchland et al., 2008). Likewise, it should also be noted that the classical coherence-dependent ramping during dots viewing is sometimes very modest relative to the overall response range of the neurons (Kiani et al., 2008; Rorie et al., 2010; Rao et al., 2012) and can exhibit idiosyncrasies (Roitman and Shadlen, 2002).

Given the large magnitude and unknown time course of this decision-irrelevant component of the response, it is important to characterize how it interacts with decision-related activity. The most obvious test would be to simply withhold presentation of the choice targets until after the moving dots. If the targets always occurred in stereotyped location, this manipulation would not exert a significant effect on behavior. However, it is far less obvious what would happen to the response dynamics during the moving dot stimulus and decision formation. If LIP really reflected a drift diffusion process (such that the spike rate mapped on to the accumulation of evidence in a fixed manner), then the LIP response should be insensitive to this manipulation, and increase to the same level as it does in a normal trial.

Alternatively, the usual levels of LIP response seen in the dots task might reflect the summed contributions of visual drive and decision-related activity. If that were the case, LIP responses might start from a considerably lower level than is commonly observed. Although it would obviously be interesting to see what happened to the downward ramps (ones associated with choices of the target outside the RF) given that they might approach zero spikes/sec, it would be perhaps more important to evaluate whether the upward ramps (associated with choices of the target in the RF) were affected by this manipulation. Other possibilities abound (e.g., an extreme example would be that the visual target gates decision-related activity through LIP)—but the key point here is simply that we know very little about some rather basic components of the sensorimotor processes reflected in LIP. If LIP implements an unwavering neural correlate of a drift-diffusion process underlying decision formation, its responses should be impressively robust to manipulations of decision-irrelevant factors that are known to exert large effects on LIP spike rates. Given that some experiments discussed above have already extended decision-related aspects of the task (i.e., the number of choice alternatives) by (necessarily) changing the visual stimulus geometry, it would be helpful to have a general analysis scheme that could parcel out the purely sensory effects of these manipulations from the changes in decision processes of interest (although some of these studies have attempted to address this issue with clever control conditions).

Another standing question has to do with the early phase of the LIP response before the ramping responses start. After the onset of the moving dots, there is an approximately 200 milliseconds-long period in which responses do not depend on motion direction or coherence, and instead undergo a roughly stereotyped dip and rise. This phase has been interpreted in many different ways—e.g., as a reset of a neural integrator (Sato and Schall, 2001; Roitman and Shadlen, 2002; Mazurek et al., 2003; Huk and Shadlen, 2005), or as a sensory or attentional interaction between the choice targets and the onset of the moving dots (Ben Hamed and Duhamel, 2002; Wong et al., 2007). Although these intriguing propositions exist, this phase of the response has received little direct experimental effort. One thing we do know is that this phase is better thought of as a latency of LIP relative to the dots, as opposed to a period of time in which the ongoing moving dot stimulus is ignored (behaviorally and neurally). The clearest evidence that this early motion matters comes from experiments that manipulated the time course of motion coherence: changes in the motion signal that occur while LIP is undergoing the dip-and-rise still affect neural responses (as well as psychophysical performance) with the appropriate 200 ms latency (Huk and Shadlen, 2005; Kiani et al., 2008). Moreover, monkeys can still perform the task above chance for very brief presentations of the dots (Gold and Shadlen, 2000, 2003).

There are some simple experiments that could shed light on the computational meaning of the dip-and-rise. If this pattern is due to a "reset," then performing a version of the dots task in which monkeys are trained to "start over" their integration later during the moving dots should create new dip-and-rises accordingly (Bennur and Gold, 2011). If this pattern is instead due to an attentional shift from the targets to the onset of the moving dots, a cue that systematically precedes the moving dots should temper or modulate the dip and rise. Likewise, if the interaction between targets and dots is more of a passive visual interaction, then simple manipulations of the relative intensities of the two types of stimuli (e.g., size, contrast) should reveal such wide-field interactions. Although these are straightforward experiments in nature, they are interesting to contemplate simply because they emphasize that we do not understand the significance of the first 200 ms of LIP response during the formation of decisions. This seems in part because the drift-diffusion framework does not naturally offer up an interpretation, other than to suggest that LIP reflects drift-diffusion with a particular latency.

In summary, there are many unanswered empirical questions within the dots task paradigm. These are rather basic questions that focus on how simple visual elements of the task drive LIP and interact with the decision-related activity. Although these may sound less lofty than the interactions between multiple cognitive factors of the sort that are currently receiving attention, we argue that understanding the basic visual components of the

task is not just a tractable exercise for characterizing basic sensory computations in LIP, but a critical underpinning for more precise interpretations of the other, less-well-understood (but perhaps more intriguing) cognitive signals seen in LIP.

IMPLEMENTATION ISSUES

LIP receives so much attention primarily because the temporal dynamics of its responses span sensory, cognitive, and motor functions. Classically, many neurons in LIP are known to exhibit strong persistent activity during memory-guided saccades. When a future saccade target flashes on the screen within the RF of an LIP neuron, the neuron responds strongly; and when the monkey eventually saccades to the remembered target location, the neuron also responds strongly. But what is more impressive is that these same LIP neurons also exhibit temporally-persistent activity that bridges the delay period between the target's flash and the memory-guided saccade.

The temporal dynamics of LIP responses during the moving-dot direction-discrimination task also suggest an important role in bridging sensory and motor functions. As described earlier, LIP responses ramp upwards or downwards over time, in a choice- and coherence- dependent manner that is consistent with the accumulation of evidence over time. Such dependencies were initially observed in "fixed-duration" versions of the task in which the experimenter presented the stimulus on every trial for a known amount of time (1–2 s) (Shadlen and Newsome, 1996, 2001). Although this was already an intriguing result, the temporal dynamics of the responses were difficult to interpret precisely, because it was not known exactly when a decision was made (and presumably, when the accumulation of evidence stopped). Therefore, later work using a free-response ("response time") version of the task yielded temporal dynamics that appeared to even more neatly line up with the accumulation of evidence leading up to a decision about motion direction (and hence to move the eyes to a particular choice target) (Roitman and Shadlen, 2002).

To test the hypothesis that spike rates in LIP reflected the temporal integration of evidence related to decision formation, a pair of studies injected brief "motion pulses" into the standard moving-dots stimulus (Huk and Shadlen, 2005; Kiani et al., 2008). These brief events serve both as a way to create a time-varying stimulus that should yield a specific change in the temporal dynamics of LIP, as well as being temporal "tags" that help disambiguate the timing of LIP responses relative to stimulus events. In the original study (Huk and Shadlen, 2005), motion pulses in either the same or opposite direction of the dots made LIP responses increase or decrease in a direction-dependent manner. Furthermore, these perturbations persisted in the LIP response for several hundred milliseconds. This was a critical result, as it provided the first direct evidence that LIP firing rate at a particular point in time was a function, not just of the current stimulus, but of the previous stimulus history (within a behaviorally relevant time frame). In other words, LIP firing rates approximated the time-integral of relevant sensory data during decision formation, and "remembered" the motion pulse. A second study (Kiani et al., 2008) extended this basic result and more quantitatively probed how these pulse effects might change over time under the assumption that evidence was not accumulated forever, but just until enough was attained to make a decision.

Although these studies serve as rigorous engineering-style assays of the time-integration properties of LIP, they shed very little light on *how* neurons might perform such temporal integration. At first glance, there appear to be two extremes of explanation: either cells are individually endowed with intrinsic biophysical mechanisms that allow them to continue responding to inputs that are no longer present, or they are situated in a circuit that creates persistent activity by virtue of its network architecture. In fact, the extremes of this dichotomy are not the only possibilities worth considering, as theoretical work has shown that both slow intrinsic time constants *and* recurrent network connectivity are likely necessary to support persistent activity that is relatively stable over appropriate timescales (Tegnér et al., 2002; Wang, 2002).

Because the long temporal integration of LIP neurons is a rather unique property compared to the more "real time" response dynamics of basic sensory and motor neurons, we propose that temporal integration *per se* deserves at least two lines of focus. First, is the temporal integration capacity of LIP neurons fixed (by virtue of the intrinsic and extrinsic factors described above), or can it vary? Second, do LIP neurons compute this time integration, or do they receive signals that are already time-integrated? A variety of experiments discussed below could answer these questions. Loosely, these can be divided into "single neuron" issues and "network" issues.

SINGLE NEURON MECHANISMS

There is already a tacit assumption that the temporal integration capacity of LIP neurons is somewhat fixed. In the context of the moving dots task, experimenters typically use the observance of persistent activity not just as a general tool for confirming that their electrode is in LIP, but also as a cell selection criterion (Shadlen and Newsome, 1996) for gathering data from neurons that will show ramping temporal integration. However, even within this selected subpopulation of LIP neurons with persistent activity, response heterogeneity is significant (Premereur et al., 2011), and many neurons exhibit weak or idiosyncratic forms of temporal dynamics that do not suggest robust or canonical temporal integration.

The application of a "robust persistent activity" criterion for choosing whether or not to perform an experiment while recording from that particular neuron reflects a strong assumption that certain LIP neurons are robust time-integrators, while others are not. By then presenting the average activity of the subset of LIP neurons with strong persistent activity as a "population response" that is a quantitative neural correlate of a decision process, it also reflects the assumption that the signals in these cells can somehow be distinguished from other signals in LIP in forming the decision. These are strong assumptions.

There are several potential ways to gain insight on these issues. First, if the temporal integration properties of cells are relatively fixed, the degree of temporal integration seen across tasks should be stable, as it would derive from an intrinsic cellular mechanism (considered in Durstewitz and Seamans, 2006). For example, if a cell exhibited robust persistent activity during memory-guided saccades, it should exhibit strongly linear ramping during the dots task. On the other hand, cells that show decaying persistent activity during memory-guided saccades might

exhibit dots-task responses that saturate. In the simplest case, the decay of persistent activity could be fit with an exponential, and the value of this time constant of decay would explain the time constant of saturation in the dots-task responses. In relevant work from a visual search paradigm, NMDA receptors (which have a distinctively long time course) have been implicated in neural temporal integration (Shen et al., 2010; see also Standage and Paré (2011) for associated modeling). It is likely that cellular mechanisms such as NMDA receptors are critical within a recurrent network architecture (Wang, 2002).

Of course, it remains to be seen whether simple characterizations of temporal integration properties are even appropriate, but the general approach holds regardless of the specific functional form needed to fit real data. Primarily, it remains to be seen whether the persistent-activity criterion is even justified. Although there are likely anecdotes and expert hunches underlying this assumption, systematic direct tests of this assumption are currently absent from the literature. The reason for this might be that one would need to record from neurons without strong persistent activity to see if they indeed did not carry decision-related activity during the dots task. Although researchers (especially ones that use animal models) are wisely cautious of performing experiments in which they expect not to see an interesting response, these measurements are a necessary part of understanding the neural computations performed by LIP neurons. It is likely that such measurements would also provide additional insights into the variety of signals carried by "non-canonical" LIP neurons, of which there are many.

This last point may be imperative for forward progress. Our understanding of early visual areas like V1 has culminated in a characterization of different cell types, which has in turn suggested distinct neural computations and even a potential hierarchy (e.g., from simple to complex cells). Despite the large amount of work in LIP, we are not close to such a nuanced answer. Although it is known that cells in LIP exhibit varying degrees of visual, memory, and motor responses (Barash et al., 1991), considerably more emphasis could be placed on understanding the single neuron computations. The vast majority of work in the dots task has focused on plots of population response, or in cell-by-cell analyses that use derived variables extracted to test a very limited hypothesis. This contrasts even with work on a related oculomotor area, the frontal eye fields, for which the appreciation and categorization of cell diversity has been a long-standing element (Bruce and Goldberg, 1985; Cohen et al., 2008).

Beyond the need for continued progress in appreciating different cell types (Premereur et al., 2011), there is relatively little fine-scale understanding of the architecture of LIP. It has been subdivided based on anatomy and connectivity into dorsal and ventral components (Lewis and Van Essen, 2000b), and one study has suggested a more "cognitive" role for neurons in ventral LIP (Liu et al., 2010). And although dots-task studies have gradually emphasized (and even targeted) LIPv, there is again very little published data that test whether decision-related signals are indeed represented preferentially in a distinct group of cells or location. This is another thorny issue to address in practice, given that with conventional single-electrode/single-neuron techniques (coupled with a dorsal-to-ventral penetration trajectory), the simple probability of encountering a desirable neuron grows over time, and in this case depth. Multi-electrode or stacked-array recordings might provide greater leverage on this issue. Some investigations of LIP cell types and circuitry have been performed using other techniques (Lynch et al., 1985; Blatt et al., 1990; Schall et al., 1995; Ferraina et al., 2002; Bakola et al., 2006), but significant progress at fine spatial and computational scales remains to be made. And analogous work in other animal models will be an important complement, given the array of powerful tools at the disposal of researchers using smaller animals (e.g., Atallah et al., 2012; Raposo et al., 2012).

NETWORK

Other implementation questions are more network-oriented. Perhaps the most glaring shortcoming in our understanding is the lack of quantified inter-neuronal correlations. The vast majority of analyses have focused on linking LIP activity *on average* with corresponding aspects of behavior. However, quantities related to the average spike rate (say, averaged over neurons, or repetitions of certain types of trials) can obscure the dynamics within the population on single trials. One bit of leverage in previous papers has involved correlating the LIP response on single trials with the reaction time of the monkey, which has often indicated a significant negative correlation (i.e., stronger responses are correlated with faster RTs; e.g., Roitman and Shadlen, 2002). However, a more direct attack will of course involve the measurement of multiple neurons simultaneously. An important first step has very recently been published that demonstrates the utility of these measurements (Bollimunta et al., 2012). Such measurements will provide a more thorough estimate of the population response within LIP on single trials (in fact, undifferentiated multi-unit "hash" may be a particularly powerful metric in this domain, although this suggestion is admittedly in tension with the prior section's emphasis on understanding single unit computations). Recent work focused in another posterior parietal region (the parietal reach region, PRR) has demonstrated the utility of moving beyond single-unit spike counts (Pesaran et al., 2002; Hwang and Andersen, 2009, 2010, 2011, 2012), as well as one study that gained leverage from distinct signals seen in local field potentials in LIP during the dots task (Bollimunta and Ditterich, 2012).

Multiple-neuron recordings also allow for the quantification of inter-neuronal correlations. Although correlation is always an important factor in understanding the amount of information that can be signaled by a neural population, it is a particularly valuable piece of information in understanding the mechanisms underlying temporal integration in LIP. Theoretical models of LIP based on recurrent connectivity (resulting in attractor dynamics) should make rather distinctive predictions for the magnitudes and time courses of neuronal correlation (Wang, 2002; Wong et al., 2007). Although initial models of LIP have assumed a fixed correlation extrapolated from measurements in sensory areas, attractor dynamics would likely be manifested in a transition from relatively weak correlations to very strong correlations at the time of decision formation.

It is also not known whether such relations are fixed properties of the network, or whether they themselves are dynamic,

depending on the nature of the task. For example, if two neurons with partially-overlapping RFs contain a shared choice target, they should function as part of the same assembly; if the task is then changed so that those same two neurons now now contain different choice targets in the non-overlapping portions of their RFs, they should now participate in competing pools (Bollimunta et al., 2012). Whether their responses and inter-neuronal correlations are fixed, or depend on such task changes, will provide important insights into the flexibility of the circuitry. In general, simultaneous multi-neuron recordings are needed for furthering our understanding of the network mechanisms in LIP. Such experiments are just starting to be reported (Bollimunta et al., 2012), and more results from this enterprise are eagerly anticipated. Similarly-minded studies have already identified context-dependent responses in related brain areas, such as MT (Cohen and Newsome, 2008).

Another more general issue that deserves more work is where LIP is situated in the decision-making circuit. Anatomical evidence provides little constraint on the circuitry, instead revealing a pattern of promiscuous, bi-directional connections between many parts of posterior parietal "association cortex" and a variety of sensory and oculomotor brain regions. An intriguing bit of physiology that should receive more attention is the pattern of latencies across brain areas. LIP itself exhibits a relatively long latency: After a 200–225 ms dip-and-rise phase that does not depend on stimulus or predict the eventual behavioral response, LIP exhibits its customary ramping activity. This is a very significant latency relative even to MT, which responds to simple visual stimuli with a lag on order of ∼80 ms (Britten et al., 1993; Raiguel et al., 1999). Thus, LIP's decision-related activity, although postulated to reflect the time-integral of relevant directional input from MT, lags behind the MT signals by at least 120 ms. So, based on simple latencies, we should assume that the circuit distance from MT to LIP is one and a half times as far as the distance from the retina to MT. Of course, assigning latencies to LIP is a somewhat dubious exercise, given that the form of its response does not have as distinct an onset as a purely sensory response. Regardless, such a ballpark analysis suggests that a variety of neural computations (and synapses across brain areas) could lie between MT and LIP. One caveat is that the latencies of other signals in MT and LIP may not follow such a simple temporal relation (Saalmann et al., 2007; Herrington and Assad, 2010).

A number of experiments have focused on recording single-neuron responses during the dots task in other oculomotor brain areas, with recent emphasis by Gold and colleagues. In short, recordings from superior colliculus, caudate, and FEF all reveal decision-related ramping responses (Horwitz and Newsome, 2001; Ding and Gold, 2010, 2011), suggesting that the signature aspects of LIP activity during the dots task may be the consequence of a distributed computation (or the widely-disseminated results of a computation). It is likely that subtleties in the relative latencies, statistical relations to behavioral variability, and qualitative effects beyond the ramping component will ultimately inform a circuit-level understanding of decisions in the dots task. For the time being, it appears that collecting more information about the responses of multiple areas, preferably under identical task conditions (and training histories) will be necessary. Comparisons between parietal and prefrontal activity have indeed begun to yield insights into working memory and oculomotor behavior (Qi et al., 2010; Katsuki and Constantinidis, 2012).

SUMMARY

This discussion reveals that the relation between LIP and the accumulation of evidence is primarily a descriptive link: one mimics the other with good fidelity under some conditions. However, we know precious little about how LIP neurons might come to reflect such temporal integration. There are both single-neuron and network measurements that are now feasible and which could begin to unpack the neural computations that underlie LIP's neural correlates of decision formation. Although continued demonstrations of such correlations in new extensions and varieties of decision-making tasks provide an important phenomenological catalog, we suggest that neurophysiology can now be the appropriate tool for identifying how such signals arise in LIP, given that these signals appear to be a crucial and basic component of the transition from sensory processing to cognition. These measurements will benefit from having a common analytical framework for extracting components of the responses and quantifying factors such as latencies.

ECOLOGICAL CONSTRAINTS

From an experimentalist's perspective, one of the most appealing aspects of the moving-dots task is that it requires hundreds of milliseconds of psychophysical deliberation. This is a long period of time to concurrently measure neural responses, allowing for insights into the time course of decision formation. Given that most visual tasks require only short (<100 ms) of temporal integration, the quarter- to half-second (or more) of decision formation time during the dots task is precious.

However, the long time course of this task raises the specter of ecological relevance. A typical trial in this task involves a few hundred milliseconds of stable fixation, a few hundred milliseconds associated with the onset of the choice targets, several hundred milliseconds of the moving dots stimulus, and sometimes a post-stimulus delay period, before the ultimate saccadic response. A trial, from start to finish, can rarely be completed in less than a second. This pacing contrasts starkly with natural oculomotor behavior, in which saccades can occur on order of 3–5 times per second (Findlay and Gilchrist, 2003).

Raising this issue is not meant as a criticism of artificial stimuli and well-controlled experiments (Rust and Movshon, 2005). However, it may not be correct to draw a full analogy between the use of bars and gratings and dots to understand sensory processing, and the use of arbitrary tasks to probe the mechanisms of cognition. Presuming that LIP also functions outside of the laboratory, it probably evolved as part of a circuit that guides saccadic and attentional exploration of visual scenes (indeed, it exhibits interpretable response patterns during relatively unconstrained oculomotor behaviors; e.g., Ipata et al., 2006). If the natural neural computations in this area guide a saccade every 200–300 ms, what do the responses of LIP neurons tell us when the monkey must maintain stable fixation (i.e., avoid doing what they would naturally do) for approximately an order of magnitude longer? (Relatedly, little is known about whether the nature of

these saccades differentially affects LIP, i.e., conventional saccades related to visual exploration, versus microsaccades).

Of course, this discussion cannot provide a definitive answer to whether the unnatural timing of saccades in the dots task can still reveal basics of function, but this point is worth keeping in mind for at least two reasons. The first is as a reminder that some of the signals inferred from LIP activity might reflect the circuit being inhibited from its natural function (for example, the timing and urgency signals posited in recent work (Churchland et al., 2008; Hanks et al., 2011) might be an inevitable consequence of the circuit "gearing up" for the next eye-movement after an unnatural period of inhibiting such behaviors). Second, this tension between experimental and natural time scales of oculomotor behavior suggests a variety of intriguing experiments that may shed light upon how to interpret responses in LIP.

If saccades typically occur several times a second, but interesting cognitive decisions require deliberation over longer periods, it is unclear what the decision-related signals seen in LIP during the dots task tell us about the general neural computations underlying the accumulation of evidence. Perhaps we are simply studying the "tail of the distribution": the mechanisms that underlie the rare moments in which primates cannot move their eyes for a second or more, but need to be planning the next eye movement (as in the case of truly "covert" attention). Relatedly, we may simply be pushing the circuit to reveal its capabilities, regardless of its modal functional time scale. However, the more exciting possibility raised by this topic is simply that LIP may carry decision-related signals that are dissociable from eye-movements.

The possibility of divorcing decision-related signals from oculomotor behavior has been raised by the results of Bennur and Gold (2011), who found that some neurons carried decision signals before an eye movement could be planned (before the mapping between moving dot direction and saccade target location was revealed). Likewise, in a task that replaced the moving dots with symbolic probabilistic cues, Yang and Shadlen (2007) showed evidence-related "steps" in LIP firing levels during the sequential presentation of stimuli (far in advance of an eye movement) that had particular log-likelihoods of reward associated with them. Other results in the literature also point in this direction, as a variety of categorization task experiments have revealed selective LIP responses that cannot be easily interpreted in terms of saccade planning (Freedman and Assad, 2009, 2011). Of course, there is also a long literature attempting to dissociate saccade intention signals from spatial attention. Also, LIP RFs exhibit anticipatory remapping, such that neurons will respond not just to a stimulus in the RF, but also to a stimulus that will be in the RF after the impending saccade (Duhamel et al., 1992). Finally, a variety of saccade metrics are not tightly coupled with LIP spike rates (e.g., Platt and Glimcher, 1999; Pesaran et al., 2002; Dorris and Glimcher, 2004; Bendiksby and Platt, 2006), even during the dots task (e.g., Shadlen and Newsome, 2001).

In summary, there is no doubt that tasks involving oculomotor responses are an effective means for eliciting strong and spatially-selective responses from LIP. Simultaneously there is a growing body of evidence suggesting that LIP can carry decision-related signals that are not tightly coupled with the plan to make a saccade into or away from the RF. However, we currently have very little leverage on understanding whether the slow ramping activity seen during the dots task—perhaps the most-studied "decision signal" in LIP—can be dissociated from the plan to make a particular saccade. Basic experiments are easy to envision, and seem particularly motivated in light of recent exciting developments that have posited a tight link between decision signals during the dots task and the recruitment of particular effectors (Resulaj et al., 2009; Selen et al., 2012). However, such experiments will entertain time scales that are shorter (e.g., natural fixation distributions) and longer (e.g., estimations of reward rates) than are commonly considered in conventional "trials," and so (just as in the prior sections) these computational questions call for an analysis approach that is general enough to model the relation between a wide array of external variables and LIP responses.

CONCLUSIONS

This discussion began by describing the face-level similarity between LIP activity during the formation of decisions in a random-dot direction discrimination task, and the psychological process of evidence accumulation hypothesized to underlie those decisions. In a quantitative sense, the average LIP response over time bore an uncanny resemblance to the sort of noisy accumulation process posited in models within the drift-diffusion framework. Since the original reports of such a "neural correlate" of decision formation in LIP (Shadlen and Newsome, 1996, 2001; Roitman and Shadlen, 2002), further work within this experimental paradigm has built a large body of correlational phenomena linking LIP physiology and the formation of decisions in the context of a drift diffusion model—and has gone on to begin using the physiology to refine and extend the classical psychological models (see Gold and Shadlen, 2007; Wong and Huk, 2008; and Churchland and Ditterich, 2012 for more comprehensive reviews).

Although this is a remarkably rigorous neural correlate, we have attempted to identify several holes in our understanding of what LIP responses mean. For example, in the empirical domain, we pointed out that it is not yet known whether LIP responses are an invariant and pure neural correlate of the accumulation of evidence, or rather whether they carry a decision-related signal that can be mixed with other (sensory and motor) signals. If the latter is true, then we must contemplate whether downstream structures can properly de-multiplex the LIP response in order to distinguish the decision signal from extraneous factors that also elicit spikes in LIP. In terms of implementation, we also noted that very little is known about how LIP responses might come to reflect the time-integral of relevant sensory evidence: is it a remarkable intrinsic property of these cells or more of a distributed network computation? Finally, we questioned the ecology of the dots task, raising the question of what the task might tell us about decision formation over time, given that it involves stable fixation for roughly an order of magnitude longer than natural oculomotor behavior involves.

In summary, there are a large number of unanswered questions, and although they fall under a wide array of rubrics (summarized above), they are all fundamentally about what and how LIP neurons compute; i.e., characterizations of the relevant

inputs, the corresponding outputs, and the basic principles that predict the outputs from inputs. The answers to these computational questions are critical for understanding what LIP does, and should also provide important links to other studies of LIP during tasks focused on shifts of attention, eye-movement planning, visual search, categorization, valuation, and other phenomena. We suggest that continued demonstrations of neural correlates of a decision variable in LIP will not answer these questions. Instead, a new analytic perspective may facilitate work that emphasizes neural computations over neural correlates. In the next section, we propose an "encoding-decoding" framework and explain why our current understanding of LIP is at a critical stage that requires it.

THE ENCODING-DECODING FRAMEWORK FOR LIP

Although LIP is intriguing because it so often appears to carry signals that are distinct from "simple" sensory and motor processes, this does not mean that the analysis of LIP responses requires novel machinery. In fact, LIP's apparent complexity may be easiest to crack if we adopt an analysis strategy that starts with an explicit focus on the observable sensory and motor elements. This leads us to what we call an "encoding-decoding" framework.

The first part, *encoding*, involves building a descriptive model of if and when an LIP neuron will fire an action potential, given various external variables. Note that although the term "encoding" is usually applied in this context to describe the role of sensory neurons, here we mean it in the more generic sense of modeling a neural response given external variables. In the case of LIP, and the tasks used to study it, there is a long list of potential factors. In even a simple version of the dots task, there are several stimuli that could drive LIP: the fixation point, the choice targets, and the moving dots. Furthermore, encoding models are not constrained to be causal, so one can also contemplate task elements that might be preceded by LIP responses, such as buildup activity preceding the saccadic eye-movement. Finally, they can be easily extended to consider factors that are outside core analyses of the dots task, but which other lines of work have suggested are important in LIP, such as rewards (or lack thereof), and the recent history of behavioral responses (or of trial outcomes). Along these lines, one underappreciated study showed the utility of this approach by decomposing LIP responses into basic three components: sensory, motor, and "cognitive" (Ipata et al., 2009). We suggest that this sort of approach can be vastly expanded and generalized within a principled statistical framework.

Of course, implementation of such a general encoding model will be nontrivial, and would require both judicious experimental design and an appropriate means for both separating the effects of all these events as well as combining them to generate a single output (spikes). Work in other systems has relied on a generalized linear model (Simoncelli et al., 2004; Truccolo et al., 2005), which involves a front end of linear filters followed by a conventional nonlinearity and a probabilistic spike generation step. Although such encoding models have been primarily applied to earlier sensory or later motor regions, their flexibility may make application to sensorimotor areas like LIP especially illuminating. In short, they would allow for letting the data (and a careful record of all potentially-relevant events) tell us what makes an LIP neuron spike, within a framework that assumes the multiple factors combine straightforwardly (e.g., obey superposition).

Regardless of implementation, a successful encoding model could yield significant insights into the neural computations performed by LIP. To start, one could ask to what degree the response of LIP is a function of the multitude of events going on in even the simplest tasks. Furthermore, each component driving the LIP response could be isolated. This would allow further analyses to focus on a particular component of interest, such as the response to the dots, as isolated from potential responses to the target and related to the impending saccade. Distinguishing these components might shed light upon the significant heterogeneity seen across LIP neurons (e.g., Barash et al., 1991; Premereur et al., 2011). Finally, another potential benefit of such an encoding decomposition would be comparisons across studies that use very different tasks: The elements that are typically shared across tasks could be distilled out (such as responses to targets and saccades), so that the remaining distinct response components could then be interpreted and compared. Ideally, an encoding model would serve as a common language for understanding which signals are present in LIP across a variety of tasks and studies—and perhaps for resolving apparent differences based on subtler differences in seemingly trivial elements, such as the timing or locations of visual stimuli (e.g., the choice targets).

The other side of this framework, *decoding*, would involve taking LIP responses and trying to infer the presence or value of some external variable. Again, for clarity, although the term "decoding" is often used in this context to describe what LIP is thought to do, here we mean it more generally, as in attempting to estimate an external event given a particular neural response. This is an important complement to the encoding perspective, especially when a brain area potentially responds to a multitude of factors in the task. For neurons that only respond to one component in a stimulus, decoding the value of that stimulus is a relatively simple complement to encoding which provides insight into the noisiness and fidelity of the representation of that feature. But for neurons whose output is the superposition of multiple factors, decoding the value of a single variable is a richer puzzle. It requires the decoder to grapple with de-multiplexing a complex neural response, and hence allows for assessment of how robust and invariant a particular neural signal is in the face of other factors also driving the neuron.

A decoding analysis in LIP will benefit from (or even require) a successful model of encoding. If the multiple signals and computations performed by (and reflected in) LIP can be accurately identified from the encoding perspective, then decoding algorithms can attempt to extract these components. The performance of such decoding efforts would allow for quantitative probing of the relation between LIP and various sensory and motor functions. For example, one could ask, within a common quantitative framework, the degree to which LIP responses reflect the direction of motion in the stimulus, versus the degree to which they reflect the decision about the direction (i.e., the saccade). In addition to establishing a common ground for such quantitative assays, an explicit focus on decoding would motivate consideration of how LIP itself might be "read out" along the oculomotor pathway (see also Mirpour and Bisley, 2012). If the

instantaneous spike rate within LIP really does directly map on to a decision variable, subsequent stages would simply need to integrate LIP responses over a brief window to estimate that rate. On the other hand, alternate (i.e., longer, and time-varying) weighting schemes might extract more information from the spike train, meaning that LIP responses would not necessarily reflect the final (or optimal) decision variable, but rather a partial sensorimotor transformation. Although these possibilities raise more questions than they answer, the value of decoding as distinct from encoding has already been appreciated in LIP: Recent work has begun to use simple decoding metrics as a way to test between different functional theories of LIP (Quian Quiroga et al., 2006).

In summary, the *encoding-decoding framework* that we make explicit here is simply an application of an already-mature approach for the study of sensory and motor function. It provides an interpretive structure that should guide experiments and analyses, but is inherently data-driven in what it reveals. It also formalizes an arena for the exchange and comparison of data across multiple studies and laboratories. The extension of this framework from sensory and motor function to that of sensorimotor integration may be especially challenging, but equally enlightening.

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Three-dimensional eye position signals shape both peripersonal space and arm movement activity in the medial posterior parietal cortex

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Research conducted over the last decades has established that the medial part of posterior parietal cortex (PPC) is crucial for controlling visually guided actions in human and non-human primates. Within this cortical sector there is area V6A, a crucial node of the parietofrontal network involved in arm movement control in both monkeys and humans. However, the encoding of action-in-depth by V6A cells had been not studied till recently. Recent neurophysiological studies show the existence in V6A neurons of signals related to the distance of targets from the eyes. These signals are integrated, often at the level of single cells, with information about the direction of gaze, thus encoding spatial location in 3D space. Moreover, 3D eye position signals seem to be further exploited at two additional levels of neural processing: (a) in determining whether targets are located in the peripersonal space or not, and (b) in shaping the spatial tuning of arm movement related activity toward reachable targets. These findings are in line with studies in putative homolog regions in humans and together point to a role of medial PPC in encoding both the vergence angle of the eyes and peripersonal space. Besides its role in spatial encoding also in depth, several findings demonstrate the involvement of this cortical sector in non-spatial processes.

Keywords: fixation depth, vergence, version, gaze, sensorimotor transformation, reaching, eye-hand coordination

INTRODUCTION

The posterior parietal cortex (PPC) of primates has been shown to be important for multisensory space representation and the control of goal directed action (Culham et al., 2006; Husain and Nachev, 2007). Traditionally, PPC has been considered a key node of the dorsal visual stream involved in the "vision for action" neural processing (Goodale and Milner, 1992). The PPC comprises the superior parietal lobule (SPL) and the inferior parietal lobule (IPL), separated by the intraparietal sulcus (IPS). The SPL of macaque monkeys encompasses several areas, as shown in **Figure 1A**. These regions include V6 and V6A in the anterior bank of the parieto-occipital sulcus (Galletti et al., 1999), the medial intraparietal area (MIP) in the medial bank of the IPS, [MIP, together with the most lateral part of V6A is included within the functionally defined parietal reach region (PRR, Snyder et al., 1997)], areas PE (area 5) and PE caudal (PEc), and PGm in the medial part of SPL (Pandya and Seltzer, 1982; Shipp et al., 1998; Bakola et al., 2010). The ventral intraparietal area (VIP), located at the fundus of IPS between SPL and IPL, can also be grouped with the SPL regions due to its functional properties (Colby et al., 1993).

The above areas form together an important network that performs the integration of visual and somatic spatial information necessary for the control of arm movements in space (Snyder et al., 1997; Buneo et al., 2002; Galletti et al., 2003; Breveglieri et al., 2006; McGuire and Sabes, 2011). **Figure 1B** summarizes the flow of information in SPL by illustrating the major connections of area V6A. This brain region receives visual information from the extrastriate areas V2, V3, V4, V6, and MST (Gamberini et al., 2009; Passarelli et al., 2011). Moreover, it receives input from areas MIP and VIP, where neurons with both visual and somatosensory sensitivity have been found (Colby and Duhamel, 1991). Additional somatosensory input may be relayed to V6A through PGm. V6A also shows strong reciprocal connections with LIP and area PG of the IPL, involved in encoding spatial parameters for ocular and manual actions (Barash et al., 1991; Heider et al., 2010). V6A, together with MIP and PEc, send a strong projection to the arm region of area F2 in the premotor cortex (Godschalk et al., 1995; Matelli et al., 1998; Raos et al., 2003). In summary, SPL areas through their reciprocal interactions, collectively process visual, somatosensory and motor information to program and control reaching movements.

The anatomical and neurophysiological evidence from monkeys is in line with data from neurological patients. Lesions in human SPL have been reported to produce deficits in the perception of the spatial relationship between objects and the subjects' own body that is manifested with inaccurate reaching movements (Critchley, 1953; Perenin and Vighetto, 1988; Wolpert et al., 1998). Furthermore, damages to SPL were shown to compromise more severely the depth component of visually guided arm movements (Baylis and Baylis, 2001; Danckert et al., 2009). The encoding by SPL of the visually guided behavior in depth has been addressed by relatively few studies (Lacquaniti et al., 1995; Bhattacharyya et al., 2009; Ferraina et al., 2009). In the PRR of

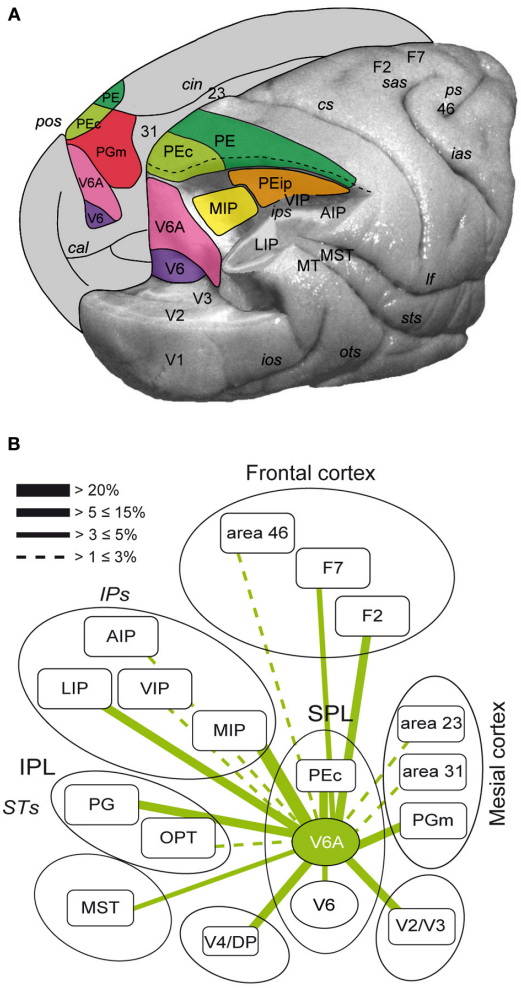

FIGURE 1 | (A) Location and extent of the areas that form the superior parietal cortex of the macaque brain. Posterolateral view of a partially dissected macaque brain modified from Galletti et al. (1996). The occipital pole has been partially removed and inferior parietal lobule of the right hemisphere has been cut away at the level of the fundus of the intraparietal sulcus to show the cortex of the medial bank of this sulcus. The occipital lobe of the same hemisphere has been cut away at the level of the fundus of the parieto-occipital and lunate sulci to show the cortex of the anterior bank of the parieto-occipital sulcus. The medial surface of the left hemisphere is drawn to show the location on it of all areas that extend medially. pos, parieto-occipital sulcus; cal, calcarine sulcus; cin, cingulate sulcus; ips, intraparietal sulcus; ios, inferior-occipital sulcus; ots, occipitotemporal sulcus; sts, superior temporal sulcus; lf, lateral fissure; cs, central sulcus; sas, superior arcuate sulcus; ias, inferior arcuate sulcus; ps, principal sulcus; V6, area V6; V3, area V3; V2, area V2; V1, area V1; PEc, area caudal PE; PE, area PE; PEip, intraparietal area PE; MIP, medial intraparietal area, PGm, area medial PG; VIP, ventral intraparietal area; LIP, lateral intraparietal area; AIP, anterior intraparietal area; MT, middle temporal area; MST, medial superior temporal area; Brodmann's areas 23, 31, 46, and dorsal premotor areas F2 and F7 in are also shown. **(B)** Flow chart of the connections of V6A modified from Passarelli et al. (2011). Rostral/caudal brain areas are shown at the top/bottom part of the figure. The thickness of the lines is proportional to the strength of each connection. Areas in the ventral part of the parieto-occipital sulcus (V6, ventral V6A) are dominated by visual input, whereas as one proceeds toward the dorsal part of V6A sensory association and visuomotor/premotor connections prevail. Inferior parietal lobule areas Opt and PG and occipital areas V4/DP are also shown.

monkeys, a strong influence of vergence angle on the activity of neurons involved in the planning of reaches has been demonstrated (Bhattacharyya et al., 2009), whereas in area PE signals related to the position of the hand prevailed (Ferraina et al., 2009).

Eye position signals are critical in the visuomotor transformations performed by the PPC, as they are used to compute the position of visual targets with respect to the body (Andersen and Mountcastle, 1983; Andersen et al., 1990; Bremmer et al., 1997). The computation of target location in an egocentric frame of reference is realized through the modulation of a visual response by gaze position in what has been referred to as a "gain field" mechanism (Zipser and Andersen, 1988). Gain fields have been demonstrated in many areas of both the dorsal and ventral stream, in the primary visual cortex and in subcortical structures as well (Salinas and Sejnowski, 2001). Regarding the encoding of target location in depth, a model of disparity-selective neurons gain modulated by the vergence angle has been proposed (Pouget and Sejnowski, 1994) and subsequent studies in PRR and lateral intraparietal area (LIP) provided experimental support for it (Genovesio and Ferraina, 2004; Bhattacharyya et al., 2009). Apart from the spatial localization of targets, gain modulations of activity by eye position have been linked with systematic biases in space representation that serve behaviorally important perceptual and motor actions. For example, in the primary visual cortex the majority of neurons that represent the peripheral visual field increase their firing as the eyes attain eccentric fixation, thus facilitating the processing of targets presented at straight-ahead directions (Durand et al., 2010). Similarly, in areas V2 and V4 most of the neurons with distance tuning for near space preferred also downward gaze positions (Rosenbluth and Allman, 2002) and this could reflect the fact that it is more usual to look down when we fixate near targets. These associations between eye position signals and behavioral context could be the result of learning and adaptation processes.

In the rest of this review we focus on the multiple functions of 3D eye position signals in SPL, in particular in area V6A. We review recent neurophysiological studies performed by our group to address whether signals related to vergence angle and to the encoding of the peripersonal space are processed in area V6A. We also present the results of studies in putative homologue regions in human SPL that also addressed these two issues. Furthermore, we will review evidence showing the influence of eye position activity on the spatial tuning of reaching discharges. In addition, we will review recent findings from human studies that support the involvement of SPL in non-spatial cognitive processes.

CODING OF TARGET POSITION IN 3D SPACE: INTEGRATION OF VERGENCE AND VERSION SIGNALS IN V6A

To estimate the position of a foveated target in 3D space, information about the direction of gaze (version) and the depth of fixation (vergence) is needed. Electrophysiological studies in various PPC areas found that neuronal activity was modulated by version signals (Andersen et al., 1990; Galletti et al., 1995; Bremmer et al., 1997; Nakamura et al., 1999). Similarly, PPC neurons affected by vergence signals were reported (Genovesio and Ferraina, 2004). In addition, vergence is a valid cue for distance estimation within the space that can be reached by the hands (Viguier et al., 2001).

A combined encoding of the direction and depth of gaze in single cells has been only demonstrated in a small number of cells in area 7a of IPL (Sakata et al., 1980).

In our study (Breveglieri et al., 2012), we set out to investigate the effect of vergence angle and its interaction with version signals in V6A. Two monkeys were trained to fixate targets located within the peripersonal space at different distances and directions from the eyes (**Figure 2A**). In total, 74% of the cells were affected by the vergence and/or the version angle, with the majority of the modulated cells being affected by both gaze variables. **Figure 2B** shows a neuron displaying its maximum discharge when the gaze was directed to the near and contralateral space. In addition, this neuron showed a linear increase of activity as the gaze shifted from far to near and from ipsilateral to contralateral positions. A multilinear regression analysis showed that in the majority of modulated neurons (∼85%) vergence and version had a linear effect on the neural activity. This finding suggests that intermediate depths and straight-ahead gaze positions did not activate maximally most of V6A cells. When the average activity of all cells modulated by vergence (**Figure 2C**, left) and version (**Figure 2C**, right) was plotted as a population spike density function, the central space evoked significantly (permutation test, $p < 0.05$) lower activity compared to contralateral and ipsilateral space (**Figure 2C**, right). At the same time, no difference was found in the average activity for near, intermediate and far positions (**Figure 2C**, left). While the underrepresentation of central gaze positions confirms studies of eye position encoding in two dimensional space (Galletti et al., 1995; Nakamura et al., 1999), the monotonic tuning of most V6A cells by vergence is a new finding that is in agreement with evidence from area LIP (Genovesio and Ferraina, 2004). At the population level, monotonic cells could equally increase their activity toward near and far peripersonal space ($n = 38$, 44% near, $n = 49$, 56% far). This result was in contrast with the study of Genovesio and Ferraina (2004), where the majority of cells increased their activity with increasing vergence. This suggests that there is a different encoding of depth in SPL compared to IPL. In neurons showing a linear effect of version there was a trend for representing contralateral space locations that was not statistically significant (χ^2 test, $p > 0.05$). In summary, our study revealed a strong effect of signals related to vergence angle in area V6A. Furthermore, these signals were often integrated with version information in single neurons thus allowing the encoding of locations in 3D space.

The putative human homologue of monkey V6A is presumably located in the dorsal part of the parieto-occipital sulcus (POs), anterior to the human V6 (Pitzalis et al., 2006; Cavina-Pratesi et al., 2010). In that region, modulations of activity by the direction of gaze (Law et al., 1998; Williams and Smith, 2010), but also by eyes' vergence have been reported (Quinlan and Culham, 2007). In the latter study, the authors found higher activity in the dorsal POs while the subjects were viewing moving or stationary stimuli located in near space, compared to the intermediate or far space. It should be noted that the intermediate spatial location was within the limits of reachable space, whereas the far location was outside of reachable space. Fixating small LEDs placed at the same range of distances (near, intermediate and far) resulted in the same pattern of modulation in dPOS. Given the consistency

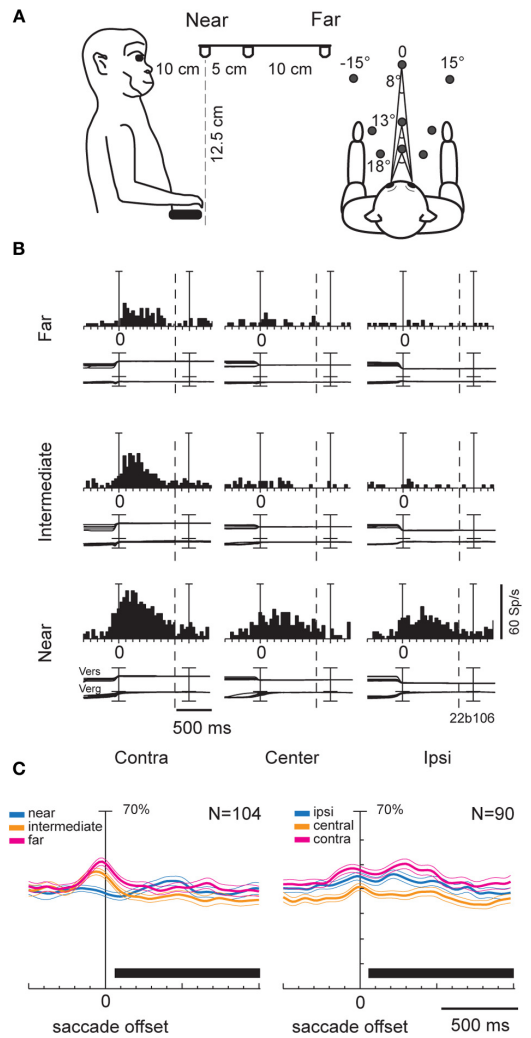

FIGURE 2 | (A) Scheme of the experimental setup set up used for the fixation-in-depth and reaching-in-depth tasks. Exact distances and angles of the targets are indicated in the lateral view (left) and top view (right), respectively. **(B)** Example of a V6A neuron modulated by both version and vergence during fixation. The discharge to the nine LEDs arranged from near (bottom) to far (top) was aligned twice (at the start of the fixation and at the LED change; dashed line: point where trials were cut because of double alignment). From left to right, the behavioral events are: LED onset, saccade offset (first alignment marker), LED change (second alignment marker). The cell has a clear preference for the near-contralateral space. Bin size for spike histograms: 20 ms; scale for version and vergence traces is 100 and 20°, respectively. **(C)** Population activity of V6A neurons modulated during fixation. Population average spike density functions (SDF) were constructed by ranking the response for each tested row of fixation targets. The thick lines indicate average normalized SDF; the light lines indicate variability bands (SEM). The peak of the SDF of the row showing the maximum activity was set to 1 (100%) and was used to normalize the SDF curves of the other rows. Activity is aligned with the offset of the saccade. The black rectangles below each plot indicate the periods where the permutation test was run. In the left plot, no statistical difference was observed between the curves (permutation test, $p > 0.05$), whereas in the right, the central row is statistically different from the other two (permutation test, $p < 0.05$). Scale on abscissa: 100 ms/division; vertical scale: 70% of normalized activity (10% per division). **(A–C)** panels were modified from Breveglieri et al. (2012).

of their results, Quinlan and Culham (2007) attributed them to the vergence of the eyes. Their findings are in line with our neurophysiological data from monkey V6A and argue strongly for the encoding of 3D space by early visuomotor areas in POs, in both human and non-human primates.

A subsequent question we examined was the influence of depth information on the reaching activity. To this end, monkeys were trained to fixate first and then reach the targets of the same experimental set up where the fixation task was performed (**Figure 2A**). **Figure 3** illustrates an example neuron recorded with the reaching-in-depth task. This neuron displayed a modulation by depth that started from movement planning and was present also during movement execution and holding of the target epochs. In all these epochs the neuron preferred far positions. In addition, during movement and target holding the cell showed a preference for central and ipsilateral targets. In most of the neurons recorded, there was an effect of both depth and direction signals in at least one motor epoch, a finding similar to the combined influence of vergence and version signals found in the fixation task (Breveglieri et al., 2012). Furthermore, the incidence and strength of depth modulations increased during the task progress. These findings suggest the presence of depth information in V6A not only for the purpose of target localization, but also for movement control (Hadjidimitrakis et al., 2011a).

Few studies have so far documented the effect of eye vergence signals in the cortex of non-human primates. Sakata et al. (1980) found in the IPL area PG-PFG cells that were modulated by both gaze direction and depth of fixation, while fewer cells were influenced by only one of these factors. Rosenbluth and Allman (2002) found that a significant number of neurons (30–50%) in visual areas V1, V2, V4 were influenced by either gaze direction, depth of fixation, or their interaction, though they did not report the number of cells affected by both signals. These areas, directly connected to V6A (see also **Figure 1B**) may be sources of vergence information to area V6A, which receives also input from the posterior parietal areas LIP and PG (Gamberini et al., 2009), where vergence angle has been reported to have an effect on presaccadic and fixation activities, respectively (Sakata et al., 1980; Genovesio and Ferraina, 2004). Other possible sources of vergence input are the medial superior temporal area (MST) and the frontal eye fields (FEF). Both regions contain neurons with vergence-related activity (Inoue et al., 1998; Gamlin and Yoon, 2000; Akao et al., 2005) and send efferent inputs to V6A (Gamberini et al., 2009; Passarelli et al., 2011). In addition, modulations of neural activity by vergence have been found in the VIP (Colby et al., 1993) and in visual areas V2 and V4 (Dobbins et al., 1998; Rosenbluth and Allman, 2002), all of them directly connected with V6A, as also summarized in **Figure 1B**. The two extrastriate areas, in particular, send strong inputs to the ventral part of V6A (Passarelli et al., 2011), so are likely candidates to provide vergence signals to V6A.

ENCODING OF PERIPERSONAL SPACE IN MONKEY AND HUMAN V6A

The space within arm's reach is also termed peripersonal space (Previc, 1998). Several lines of evidence from monkey neurophysiology seem to support the view that the encoding of peripersonal space is being processed in PPC, and more in particular in SPL. For instance, neurons with multimodal (e.g., visual-tactile) receptive fields (RFs) have been reported in several PPC areas (Colby et al., 1993; Avillac et al., 2005). Overrepresentation of body

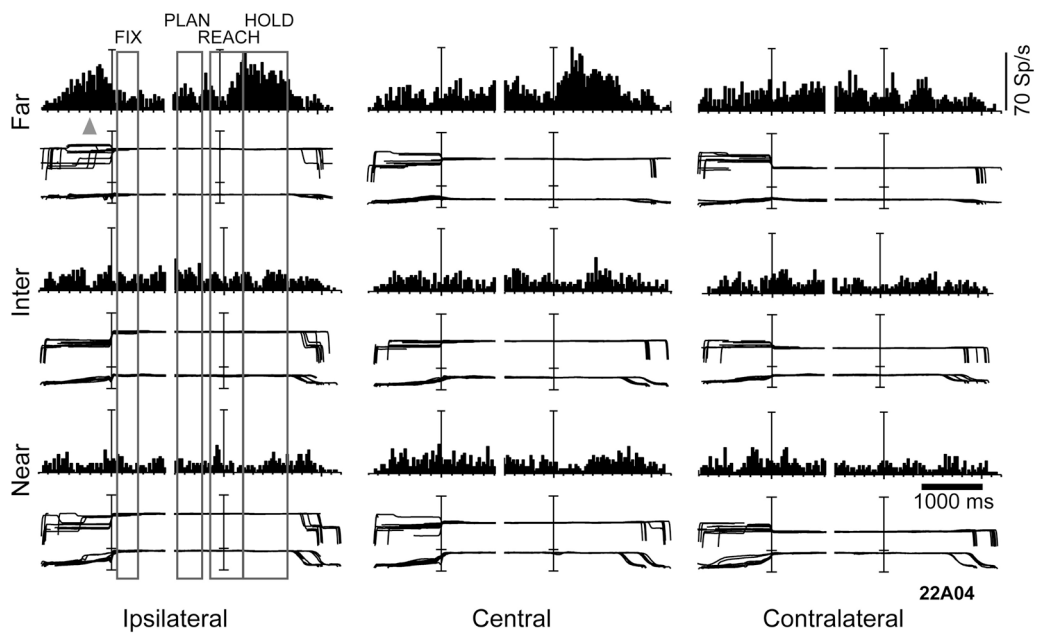

FIGURE 3 | Example of a V6A neuron modulated by depth and direction signals during several epochs of a reaching-in-depth task. Target LEDs were arranged as in **Figure 2B**. Spike histograms and eye traces were aligned twice, at the fixation onset and at the start of movement. This cell prefers far space during movement planning, execution and holding of the target epochs. In the last two epochs it was also tuned for ipsilateral space. The gray triangle indicates the mean time of LED onset. Bin size for spike histograms; 20 ms; scale for version and vergence traces is 100 and 20°, respectively.

parts (e.g., face or hand) (Colby et al., 1993; Breveglieri et al., 2002; Graziano and Cooke, 2006) that are behaviorally important has been found in several SPL areas and these representations show adaptation after training or are modified depending on the task performed (Graziano et al., 2000). In addition, representational biases in the encoding of visual space could be attributed to the natural position of the effectors in space. In this context, areas of the dorsal visual pathway show a preferential encoding of the lower visual field where the hands are usually located (Previc, 1998). Area V6A belongs to the dorsal pathway and the vast majority of V6A neurons have their visual RFs in the lower contralateral visual field (Galletti et al., 1996, 1999). In addition, many V6A neurons have somatosensory RFs centered on the arm (Breveglieri et al., 2002) and even more show spatially tuned responses during reaches in 3D space (Fattori et al., 2005). Recently, the orientation of the hand and the type of hand grip were found to affect the activity of V6A cells during reach-to-grasp movements (Fattori et al., 2009, 2010).

The hypothesis that SPL could process specific information related to the peripersonal space prompted us to study (Hadjidimitrakis et al., 2011b) whether there is a preferential encoding of that part of space compared to the extrapersonal space in V6A. To test this, we studied the oculomotor and fixation responses of V6A neurons to targets presented at near and far parts of space. We adopted an experimental configuration used in several human studies (Gallivan et al., 2009, 2011) with small LED targets arranged in a horizontal board below eye level, in order to simulate the natural perimanual space. The monkeys were trained to direct their gaze to the LED targets located in different positions in the 3D space without performing any arm movement (**Figure 4A**). Ten targets were divided into two rows, one located centrally, in the mid-sagittal plane, and the other located contralateral to the recording site, in a parasagittal plane (**Figure 4A**). In several neurons where isolation was held constant for longer periods, the horizontal board was translated so the targets were distributed between the central row and a parasagittal row in the ipsilateral space. Even though no reaches were performed by the animals, we checked that the two nearest LED targets in each row were within reaching distance (<30 cm).

Neural activity was quantified in a time epoch around the saccadic eye movement (perisaccadic activity) and during the subsequent fixation period (fixation activity). A One-Way ANOVA test performed independently in each row showed, on average, a significant effect ($P < 0.05$) of the depth of fixation in perisaccadic and fixation epochs in about 30 and 40% of V6A cells, respectively. About 15% of the cells were modulated by the depth of fixation in both epochs. **Figure 4B** shows the firing activity of a neuron with a tonic pattern during fixation. The greatest activity was evoked while the eyes were fixed on the nearest target, irrespectively of gaze angle (**Figure 4B**). Activity consistently decreased when fixation was directed to targets located farther and farther. In addition, at constant fixation depth the responses showed an increasing trend from contralateral to ipsilateral space (**Figure 4B**). Thus, the neuron was significantly modulated by the depth of fixation and displayed monotonic tuning for near and ipsilateral space (ANOVA, $P < 0.05$). We applied a Bonferroni *post hoc* test on the ANOVA significant cells to define the preferred position in depth in each part of space. Perisaccadic activity (**Figure 4C**, left), was typically higher for saccades to the two nearest targets: 60–75% of the cells preferred one of these LEDs in the different rows. We compared the incidence of preference for the two nearest (reachable) targets with the three that were outside the peripersonal, reachable space. The preference for reachable locations was highly significant (χ^2 test, two nearest LEDs against the three farthest ones, $P < 0.0001$). In neurons with modulation during fixation, there was also a strong preference for the peripersonal space (**Figure 4C**, right). Their percentage ranged from 65 to 74% depending on the different parts of space tested: 74% (45/61) for straight-ahead, 73% (56/77) for contralateral and 65% (19/29) for ipsilateral locations. The preference for fixating targets placed within the reachable space with respect to those positioned outside was again highly significant (χ^2 test, two nearest LEDs against the three farthest ones, $P < 0.0001$). It was also demonstrated that the fixation distance of 45 cm (third LED in each row), which was outside the monkey's reachable space, was the least represented in our cell population (**Figure 4C**, right). This "gap zone" of fixation preference, between the reachable and unreachable space, could serve to signal targets that are definitely within or beyond reach. Overall, at the population level perisaccadic and fixation activity of V6A neurons showed a strong bias for representing the 3D space within reaching distance (**Figure 4D**).

Our study showed many similarities with a human functional imaging study performed by Gallivan et al. (2009). They used an experimental setup similar to ours with objects being placed in the perimanual space, below eye level. The authors reported that passive viewing of reachable objects evoked higher activity compared to objects located in non-reachable space in the superior part of parieto-occipital cortex (SPOC). The SPOC, which was also activated during arm reaching movements (Cavina-Pratesi et al., 2010), includes the cortex anterior to the human homologue of V6 (Pitzalis et al., 2006), i.e., the putative area V6A. In that study, the fixation point was kept constantly at far locations. Objects within reachable space evoked stronger activation in SPOC, and it was suggested that this modulation could be related to the objects' reachability. The authors proposed that a reachability signal could be extracted in SPOC by the combination of gaze and object depth signals. Given the response properties of cells modulated by depth described in our study (Hadjidimitrakis et al., 2011b), it is likely that both human SPOC and macaque V6A encode the difference in depth between current fixation and location of objects to be grasped. In this context, the abundance of strong tuning for near space observed could be a result of an adaptive cognitive mechanism that satisfies two conditions: the natural tendency for fixating far and the necessity to respond to behaviorally relevant stimuli appearing in the near space. Beyond this hypothesis, both our study (Hadjidimitrakis et al., 2011b), and that of Gallivan et al. (2009) suggest that in V6A visual, eye position and motor related information is integrated to encode more cognitive variables such as motor affordance and/or potential actions (Andersen and Cui, 2009; Cisek and Kalaska, 2010; Macaluso and Maravita,

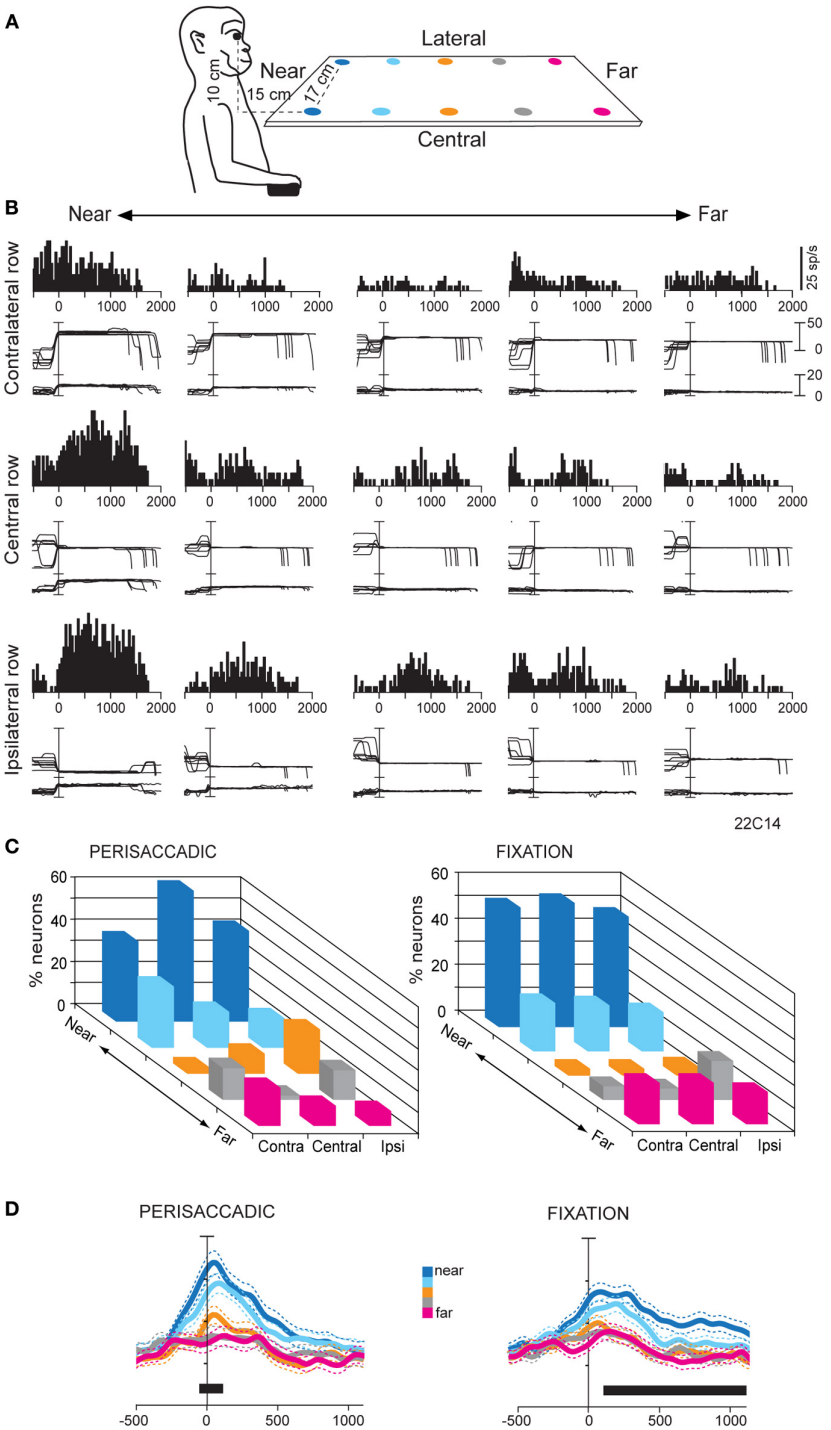

FIGURE 4 | (A) Scheme of the set up used for the fixation-in-depth task below eye level. The monkey was fixating in darkness one of the LEDs embedded in each panel. The LEDs are depicted with different colors according to their distance from a frontal plane passing from monkey's eyes. **(B)** Example of a V6A neuron modulated by vergence during fixation below eye level. Top/Middle/Bottom: neural responses (peristimulus time histograms) and eye traces to the five LEDs of the contralateral/central/ipsilateral space arranged from near (left) to far (right), aligned at the end of the saccade. This cell prefers targets located at near and ipsilateral space. Other conventions as in **Figure 3**. **(C)** Frequency histogram of the positions that neurons preferred in perisaccadic ($N = 91$) and fixation ($N = 167$) epochs. Ipsi and Contra indicate fixation position with respect to the recording hemisphere. Center refers to the straight ahead of the monkey. In both epochs there is a clear preference for near, reachable targets across all space. **(D)** Population activity for each target position, illustrated with a different color, of V6A neurons with activity modulated during perisaccadic (left) and fixation (right) epochs. Activity is aligned on the saccade onset in both panels. Other conventions as in **Figure 2C**. **(A–D)**: Adapted from Hadjidimitrakis et al. (2011b).

2010). In line with this, there is evidence from a subsequent study by Gallivan et al. (2011) that activation in SPOC region was found to be correlated with the hand dominance, with the later being crucial in defining the subjects' typical reachable space.

CONGRUENCE OF THE SPATIAL TUNING BETWEEN FIXATION- AND REACHING-RELATED ACTIVITY

As described in the previous section, neural discharges during the presentation and ocular fixation of targets can be an important cue to estimate whether they are reachable or not. But what happens when an arm reaching movement is actually performed? Does the activity during arm movement show the same spatial tuning with that of the visual fixation-related discharges? It has been suggested that PPC neurons integrate spatially consistent retinal, eye and hand information into a "global tuning field, GTF" (Mascaro et al., 2003). This type of common tuning of different effectors could be advantageous for the control of eye-hand coordination. According to Caminiti and colleagues, optic ataxia could be the result of the breakdown of GTF in SPL (Battaglia-Mayer and Caminiti, 2002). Evidence for neurons with consistent spatial tuning between eye position, arm movement and position signals has been reported in the SPL (Battaglia-Mayer et al., 2001). In that study, in a center-out reaching task about 60% of the neurons showed GTF in several epochs and across various oculomanual tasks. The same group found in area 7A a much lower incidence (∼25%) of cells with GTF (Battaglia-Mayer et al., 2005).

We addressed this issue in another study of our group (Fattori et al., 2005), where monkeys were trained to perform 3D reaching movements toward foveated LED targets arranged on a plane (**Figure 5A**). The monkeys were required to fixate the targets and wait for a go cue signal (LED color change) to perform a body-out reach toward the LED and hold it for a variable time, till another cue (switching off of the LED) signaled the monkey to return to the initial hand position. Many neurons in V6A were spatially tuned (One-Way ANOVA, $P < 0.05$), both during the outward movement execution (**Figure 5B**, Raw M1) and in the holding of target period (**Figure 5B**, Raw HOLD). Modulations in these two periods often coincided and in many cases they were spatially consistent. **Figure 5C** shows an example of this pattern of activity in a neuron that fired strongly not only when the hand moved, but also when it held targets located on the right. In addition, this neuron showed a preference for right space in the fixation period, i.e., it displayed a pattern of activity similar to the cells with GTF. To test whether the tuning of arm-related activity could be explained by gain modulation by eye position, fixation activity was substracted from the discharges in movement and hold epochs. An ANOVA ($P < 0.05$) then was performed to detect significant effects of target position on the residual firing activity. The substraction of fixation activity abolished the spatial tuning in about one-third of V6A neurons in both movement and holding periods (**Figure 5B**, Proper M1, Proper HOLD), whereas about 40% of the V6A maintained their spatial tuning. In line with our data are those obtained in area 7A in IPL (Heider et al., 2010). The authors, using a body-out reaching task very similar to ours, found that about 60% of the neurons changed their directional tuning from eye fixation till preparation and movement execution (Heider et al., 2010). Both their results and ours suggest that "global tuning" is probably implemented in PPC, but in a much more limited extent with respect to the one originally reported (Battaglia-Mayer et al., 2001).

Regardless of its incidence in the PPC, the concept of GTF has some interesting cognitive aspects. In everyday life and under certain conditions, when we want to reach and/or grasp an object, the eyes fixate on the target first and then the hand starts to move (Land et al., 1999; Hayhoe et al., 2003). In this context, the common spatial preference for eye and arm could be the result of a learned association between eye position and arm movement signals. Learning could be the result of many repetitions of combinations of eye and arm positions in space. The spatial coincidence would reinforce the response of neurons that are tuned (Ahissar et al., 1992; Rosenbluth and Allman, 2002). As a result, in these neurons, whenever the eyes move to a certain location, a plan that would carry the arm in the same location is formed. In this way, eye position signals can predict the sensory consequences of future motor actions (Land and Furneaux, 1997).

NON-SPATIAL PROCESSING IN HUMAN SPL

Apart from its crucial role in spatial perception and visually guided motor action, experimental evidence accumulated over the past decade suggests that PPC is also involved in non-spatial, higher order cognitive functions. Such functions include attention, categorization, reward, working memory, encoding of task rules, and behavioral context (for references see Culham and Kanwisher, 2001; Husain and Nachev, 2007; Gottlieb and Snyder, 2010). Most studies of cognitive processes in monkeys and humans have found the neural substrate of these functions to be located in areas of the IPL and this created a view of a gradient of increasing non-spatial, cognitive processing going from SPL to IPL (Husain and Nachev, 2007). Here, without claiming the opposite to this view, we focus on evidence that relates the SPL activity to cognitive processing.

Yantis and colleagues identified a region in the medial SPL of humans that was transiently activated during shifts of spatial attention (Yantis et al., 2002). In that study, subjects were presented with two stimulus streams of numerical cues at opposite peripheral locations (left-right). Their task was to attend one of the two streams for the presentation of a cue that signaled them, either to shift their attention to the unattended stream, or to maintain it on the attended one. The authors found that a region in the medial SPL showed a transient activation during the shift of attention, irrespectively of the direction of the shift. This area is likely homologous to macaque V6A, where modulations during covert shifts of attention have been reported (Galletti et al., 2010). Furthermore, in subsequent studies, the same human medial SPL region was found to exhibit transient activity in a variety of conditions: during non-spatial shifts of attention between objects, features and working memory representations, and during shifts between visual features that represented different categorization rules (Chiu and Yantis, 2009; Esterman et al., 2009). These findings suggest that SPL activity is related to the encoding of the change in task demands. In line with this assumption are the results of human studies performed by other groups.

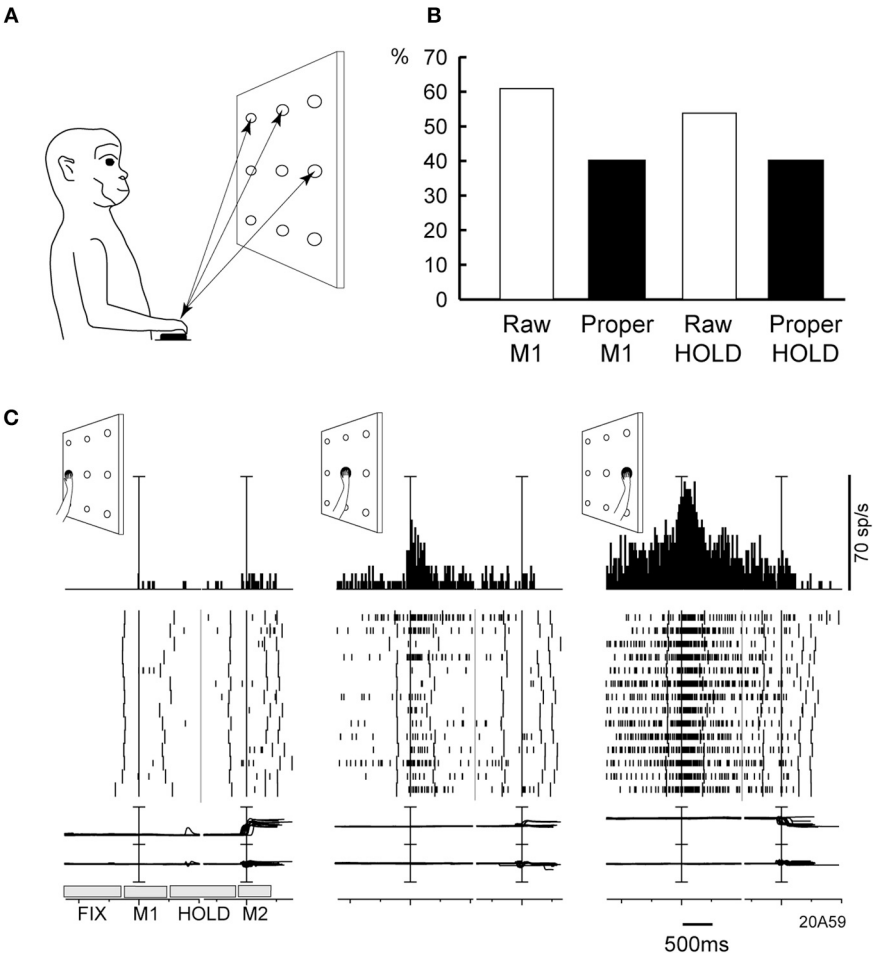

FIGURE 5 | (A) Experimental set-up and time course of a frontal reaching task. Reaching movements were performed in darkness, from a home-button (black rectangle) toward one out of nine targets (open circles) located on a panel in front of the animal. **(B)** Incidence of V6A cells spatially modulated in the reaching task. Columns indicate the percentages of spatially modulated V6A cells during outward reaching movements (M1), and static position of the arm in the peripersonal space (HOLD). "Proper" activity = "raw" activity – FIX activity. **(C)** Example of spatially tuned modulation of reach-related activity. Neuron spatially tuned in M1, preferring rightward M1 movements. Neural activity and eye-traces have been aligned twice in each inset, with the onsets of outward (1st) and inward (2nd) reach movements. The mean duration of epochs FIX, M1, HOLD, M2 is indicated in the bottom left inset. Behavioral markers on rasters from left to right: LED color change, outward movement onset, outward movement end, LED offset, inward movement onset, inward movement end, end of trial. Bin size in peri-event time histograms: 15 ms; eye traces: scale bar, 60°. Other details as in **Figure 2**. Modified from Fattori et al. (2005).

Kanai et al. (2010) observed that the perceptual switch rate between bistable structure-from-motion stimuli in humans was correlated with macroscopic anatomical features of an SPL area that mostly corresponded with the region identified by Yantis and colleagues.

Recent evidence suggests that SPL is also recruited in tasks involving working memory. Koenigs et al. (2009) found that humans with lesions in SPL displayed deficits in working memory tests that required the manipulation and rearrangement of working memory, but not the simple retrieval of it. The authors found that the manipulation in the working memory was impaired not only for visuospatial stimuli, but also for verbal-auditory ones. Furthermore, their findings are consistent with a meta-analysis of several neuroimaging studies that highlighted the involvement of SPL in the updating of the working memory (Wager and Smith, 2003). Finally, activity in SPL has been linked with mental navigation (Ino et al., 2002) and visuomotor learning (Inoue et al., 2000). In summary, the above studies strongly suggest that beyond its role in goal directed motor behavior, the cortex of SPL is also involved in processing cognitive information to enable the perception of a continuously changing environment.

CONCLUSION

In this review we have presented evidence that the cortex of the SPL, in particular area V6A processes signals related to eye position in depth. We showed that these signals can be used in simple spatial computations like the encoding of the location of visual targets in 3D space, but also in more "cognitive" ones, like the encoding of peripersonal space in terms of reachability by the arm. In addition, we reviewed studies in humans that suggest the

involvement of SPL in other cognitive processes. Overall, these findings rather than challenging the classic view that SPL play a role as an interface between sensory information and motor action, highlight the fact that this interface shows a remarkable flexibility and is influenced by attention, learning, and other cognitive factors.

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Thinking in spatial terms: decoupling spatial representation from sensorimotor control in monkey posterior parietal areas 7a and LIP

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Perhaps the simplest and most complete description of the cerebral cortex is that it is a sensorimotor controller whose primary purpose is to represent stimuli and movements, and adaptively control the mapping between them. However, in order to think, the cerebral cortex has to generate patterns of neuronal activity that encode abstract, generalized information independently of ongoing sensorimotor events. A critical question confronting cognitive systems neuroscience at present therefore is how neural signals encoding abstract information emerge within the sensorimotor control networks of the brain. In this review, we approach that question in the context of the neural representation of space in posterior parietal cortex of non-human primates. We describe evidence indicating that parietal cortex generates a hierarchy of spatial representations with three basic levels: including (1) sensorimotor signals that are tightly coupled to stimuli or movements, (2) sensorimotor signals modified in strength or timing to mediate cognition (examples include attention, working memory, and decision-processing), as well as (3) signals that encode frankly abstract spatial information (such as spatial relationships or categories) generalizing across a wide diversity of specific stimulus conditions. Here we summarize the evidence for this hierarchy, and consider data showing that signals at higher levels derive from signals at lower levels. That in turn could help characterize neural mechanisms that derive a capacity for abstraction from sensorimotor experience.

Keywords: spatial cognition, spatial attention, area 7a, LIP, parietal cortex, object-centered, constructional apraxia, navigation

INTRODUCTION

Human cognition, or in colloquial terms, thinking, is notoriously difficult to define. However defined, thinking has to be a property of neurons, and it might be possible to infer several basic and simple features of the neural mechanisms responsible without a final or complete description of the cognitive processes themselves. For example, it seems impossible to provide any biological account for thinking without patterns of activity in the cerebral cortex exhibiting the property of sensorimotor independence. That is, in order to think, the brain must be able to internally generate a sequence of patterns of neuronal activity that encode behaviorally useful information independently of concurrent sensory or motor processing. Sensorimotor independence, as we will refer to this property, seems a necessary starting point (without which thoughts would be confined to the set of current stimuli and actions). Second, it seems reasonable to assert that in many primates (including humans) some forms of thinking, associated with the intelligent control of behavior, involve abstraction (Miller, 2000; Tenenbaum et al., 2011). More specifically, the brain has to be able to generate patterns of neuronal activity that encode a particular type or class of information, best characterized by the property of generalizability. Neural signals engaged in abstraction encode regularities, relationships, or principles of general applicability that apply to a wide variety of particular sensory or motor conditions, and that capability at the single neuron level is likely to enable the brain to predict outcomes based on principles applied in novel circumstances, one of the defining central characteristics of intelligence.

The purpose of this review is to evaluate what we know about abstraction and sensorimotor independence specifically as it applies to the internal representation of space by neurons in the posterior parietal cortex of non-human primates. Available experimental evidence obtained from single neuron recording studies in parietal cortex has documented a rich diversity of spatial representations that should facilitate investigation into the neural mechanisms by which abstraction and sensorimotor independence are built on top of, or derive from, more basic sensorimotor signals in the brain. For example, a long experimental history has established the strong relationship between neural activity in the parietal cortex and the representation of spatial information that either derives from sensory input or that predicts forthcoming movement. The relative importance of visual processing and motor processing in parietal cortex has been debated for more than 30 years (see below), but there seems some consensus that

parietal cortex is interposed between sensory input and motor output and is likely to play a role converting sensory representations into motor representations. Second, a number of recent studies have shown that under certain circumstances, the same neural architecture that mediates spatial sensorimotor control is also capable of mediating spatial cognition. These data show that when confronted by more complex spatial problems, (such as those which require analyzing spatial relationships or computing spatial categories, for example), parietal neurons exhibit new forms of spatial representation more closely related to spatial reasoning or spatial problem solving than spatial sensorimotor control. Because spatial representations within parietal cortex span the range from concrete sensorimotor to abstract cognitive, parietal cortex offers a unique opportunity to gain insight into one of the most basic questions in cognitive neuroscience: how neural systems that perform a specific role in sensorimotor control acquire the capacity for abstraction and sensorimotor independence. The answer to that question is likely to lead to a greater understanding of how human intelligence emerged within a sensorimotor architecture such as the cerebral cortex.

The review is divided into four sections. The purpose of the first three sections is to review the evidence that three distinct types of neuronal signals coding spatial information coexist within posterior parietal cortex that can be considered to constitute the levels of a hierarchy of spatial representation. (The hierarchy is defined by the nature of the spatial information encoded at each level rather than then the neuronal populations engaged, to acknowledge that single neurons can carry a mixture of signals and participate at multiple levels of representation.) At the first level (which we refer to as first order spatial coding), neural signals encode stimulus attributes and movement parameters, and spatial processing faithfully reflects ongoing sensorimotor control. This is exemplified by the familiar spatial tuning of single neuron activity for stimulus position or movement direction, and the population representation of these parameters (Mountcastle et al., 1975, 1981; Georgopoulos et al., 1982, 1988; Andersen et al., 1985; Schwartz et al., 1988), which together probably represent the most behaviorally crucial forms of spatial representation in the brain. At the second level (second order), the spatial information coded by neural activity retains its dependence on stimulus attributes (such as position) and movement parameters (such as direction), so from a spatial perspective, activity does not exhibit sensorimotor independence. However the duration and intensity of these signals are modulated as a function of cognitive factors. Working memory, attention, motor planning, and decision-processing can all be characterized as instances of second order spatial processes on that basis. At the top level, neural activity encodes spatial information that exhibits complete sensorimotor independence, in both temporal and spatial domains. At this level, neurons carry signals that convey abstract, generalized spatial information, such as spatial relationships or spatial categories that generalize across numerous stimulus configurations, and no longer pertain to specific stimuli or movements. After considering the evidence that all three types of spatial representation coexist in posterior parietal cortex, we will address (see section "Origin of third order spatial representations") how abstract spatial information encoded at upper levels of this hierarchy might derive from transformations applied to spatial information present at lower levels, and speculate as to what the neural mechanisms that mediate interactions between these levels of processing might be. The issue of how signals that reflect more abstract forms of cognition emerge in sensorimotor control networks (such as the posterior parietal cortex or the cortex in general), perhaps as a consequence of sensorimotor experience, is an important question, though relatively little is presently known in terms of underlying neural mechanisms. We hope that dissociating stages and types of spatial codes that exist within parietal cortex may facilitate discovering more about how they are generated by an interaction between the neural systems of the cerebral cortex and a spatially structured environment.

FIRST ORDER SPATIAL CODING: SENSORIMOTOR CONTROL IN POSTERIOR PARIETAL AREAS 7a AND LIP

We focus the review on experimental data obtained in two adjacent parietal subdivisions, area 7a, which is located in the posterior part of the inferior parietal lobule, and area LIP, in the lateral bank of the intraparietal sulcus. A number of studies investigating the neural mechanisms of spatial cognition in parietal cortex in monkeys have focused on these two areas, providing a good basis for a comparison between cognitive and sensorimotor information processing within them.

Area 7a

Area 7a is located in the posterior aspect of the inferior parietal gyrus in monkeys. Recent work in this area has focused on its role in various forms of spatial cognition (attention, working memory, and more abstract processes), but its direct involvement in basic visual processing, specifically spatial visual processing, has been firmly established by prior research. (The role of area 7a in motor processing is less well-understood). For the purpose of establishing the coexistence of sensory and cognitive signals coding spatial information in this area, we briefly review some of the evidence indicating involvement of area 7a in first order spatial coding in the visual modality. The defining characteristic of the visual sensory responsiveness of area 7a neurons is that neuronal activity is tuned primarily with respect to the spatial attributes of visual stimuli—where they are located on the retina and how they are moving. Area 7a neurons can often be robustly driven by visual stimuli independently of cognitive factors. The visual receptive fields of 7a neurons are large and in many cases bilateral (Blatt et al., 1990), and can be driven either by stationary visual stimuli (Yin and Mountcastle, 1977; Robinson et al., 1978; Motter and Mountcastle, 1981; Mountcastle et al., 1981; Constantinidis and Steinmetz, 2001a, 2005) or moving visual stimuli (Motter et al., 1987; Steinmetz et al., 1987; Merchant et al., 2001, 2003, 2004a,b; Raffi and Siegel, 2007). Motion sensitive receptive fields of area 7a neurons often exhibit a radial arrangement of preferred directions throughout their receptive field (Motter and Mountcastle, 1981; Steinmetz et al., 1987), such that these neurons are maximally activated by either expanding or contracting patterns of optic flow (Siegel and Read, 1997; Merchant et al., 2001, 2003; Raffi and Siegel, 2007), as occurs when the observer moves through a fixed visual environment. It has been recently noted that visual motion information in parietal area 7a could

be used to derive the positions of visual landmarks and the location of the observer with respect to those landmarks, a type of spatial processing important for navigation and spatial orientation (Kravitz et al., 2011). Collectively these data indicate that area 7a neurons carry a rich array of physiological signals encoding spatial attributes of visual stimuli even under conditions (in many cases) where those stimuli are passively presented and do not have a direct behavioral or cognitive significance. As discussed in subsequent sections these signals are frequently modulated by cognitive factors, but cognitive processing *per se* is not a necessary precondition for the activation of area 7a neurons by visual stimuli.

Visual neurons in area 7a exhibit another characteristic that provides substantial insight into the spatial functions of parietal cortex in general. Many area 7a neurons exhibit gain fields (Andersen and Mountcastle, 1983; Andersen et al., 1985, 1990b), the term given to describe the influence of eye position on visual sensitivity. These neurons possess visual receptive fields that remain fixed in position in relation to the fovea, but the sensitivity of the receptive field is a systematic function of the position of the eyes in the orbits at the time that the visual stimulus is delivered (Andersen and Mountcastle, 1983; Andersen et al., 1985, 1990b). This provides an example of parietal neurons integrating diverse types of sensory information to construct superordinate spatial representations—body-centered spatial representations in this case (Andersen, 1997)—which can then be used to direct movement (Andersen and Buneo, 2002; Buneo and Andersen, 2006). The visual sensitivity of area 7a neurons is modulated not just by eye position but by other postural factors, such as the position of the head with respect to the environment, a type of spatial tuning that could help to construct a "world-centered" representation of space (Snyder et al., 1998b). Spatial representations of this class, specifying the location of visual targets relative to the body, or the world, constructed by integrating information that derives from the retina as well as a variety of somatosensory sources, has direct utility for the visual control of movement. From this perspective then, posterior parietal cortex is a prototypical sensorimotor cortex.

Area LIP

The lateral intraparietal area (LIP) is located just medial to area 7a, in the lateral bank of the intraparietal sulcus. This area was first identified on the basis of its particularly strong anatomical connection with the frontal eye fields and the presence of neurons with presaccadic activity (Andersen et al., 1990a). Subsequent neural recording experiments have confirmed a role in saccade control. Many LIP neurons are activated before the initiation of saccades and their firing rate varies systematically as a function of saccade direction (Barash et al., 1991). In the case that the saccade is delayed for several seconds after the disappearance of a visual target, LIP neurons maintain spatially selective activity for the intervening working memory period until the saccade is executed (Gnadt and Andersen, 1988; Chafee and Goldman-Rakic, 1998). Although it can be problematic to dissociate visually evoked activity from motor-related activity when movements are made toward visual targets, (or to dissociate motor plans from spatial attention under these circumstances), the activity of many LIP neurons maintains a relationship to the direction of the forthcoming saccade in double-step tasks in the case that no visual stimulus appeared in the movement field of the neuron (Mazzoni et al., 1996). This demonstrates that a visual stimulus is not necessary for LIP neurons to exhibit spatially selective activity, as is further indicated by the finding that LIP neurons are active before memory-guided saccades to auditory stimuli (Stricanne et al., 1996). Moreover, the activity of LIP neurons is frequently effector specific, and is greater when monkeys plan and execute saccadic eye movements than when they make reaching arm movements to the same visual targets (Snyder et al., 1998a; Quian Quiroga et al., 2006). Neurons in the parietal reach region (PRR) in the medial bank of the intraparietal sulcus are likewise effector specific, but are more strongly activated before arm movements than saccades. Interestingly, neural activity in these two structures is modulated as a function of which effector monkeys autonomously decided to move to a cued spatial location under conditions in which they randomized their choice of effector (Cui and Andersen, 2007). **Figure 1**, taken from (Cui and Andersen, 2007), illustrates this phenomenon. Following the initial visual transient, which was of comparable magnitude regardless of the effector selected, activity in the LIP neuron was higher on trials that the monkey decided to make a saccade to the remembered target location (**Figure 1A**; red trace), in comparison to when it decided to make a reach to the same location (**Figure 1A**; green trace). Activity in the PRR neuron exhibited the converse pattern, and was more strongly active on trials that the monkey decided to make an arm movement (**Figure 1B**; green trace) rather than a saccade (**Figure 1B**; red trace). Because visual stimulation and attention are likely to be comparable whether a monkey executes a saccade or a reach to the same visual target, effector specificity argues that visual input and attention alone cannot entirely account for the activity of LIP (and PRR) neurons.

A selective relation between LIP activity and saccades is further documented by the finding that these neurons are more strongly driven by central cues that instruct saccades vs. reaching arm movements, even in the case that the direction of the eye movement is not known prior to the appearance of the central cue (Dickinson et al., 2003). Spatial coding of saccade direction in LIP is also modulated by eye and head position, suggesting that LIP contributes to body-centered representations of space (Snyder et al., 1998b), and there is evidence that this spatial representation is three dimensional (Gnadt and Mays, 1995) and is topographically organized (Blatt et al., 1990; Patel et al., 2010; Savaki et al., 2010). Finally, it is possible to trigger saccades by electrical microstimulation of area LIP (Thier and Andersen, 1998), though higher currents are typically required in comparison to the frontal eye fields. A role for LIP in saccade control is generally consistent with its connectional anatomy. LIP output projections target saccade-related structures such as the frontal eye fields (Cavada and Goldman-Rakic, 1989b; Blatt et al., 1990) and the superior colliculus (Pare and Wurtz, 2001). The nature of that role—whether to select visual targets or spatial locations to guide downstream oculomotor structures or to provide an explicit motor command itself—though, remains a point of controversy. However, if an area codes spatial information that is dedicated to a particular motor output pathway (such as one that

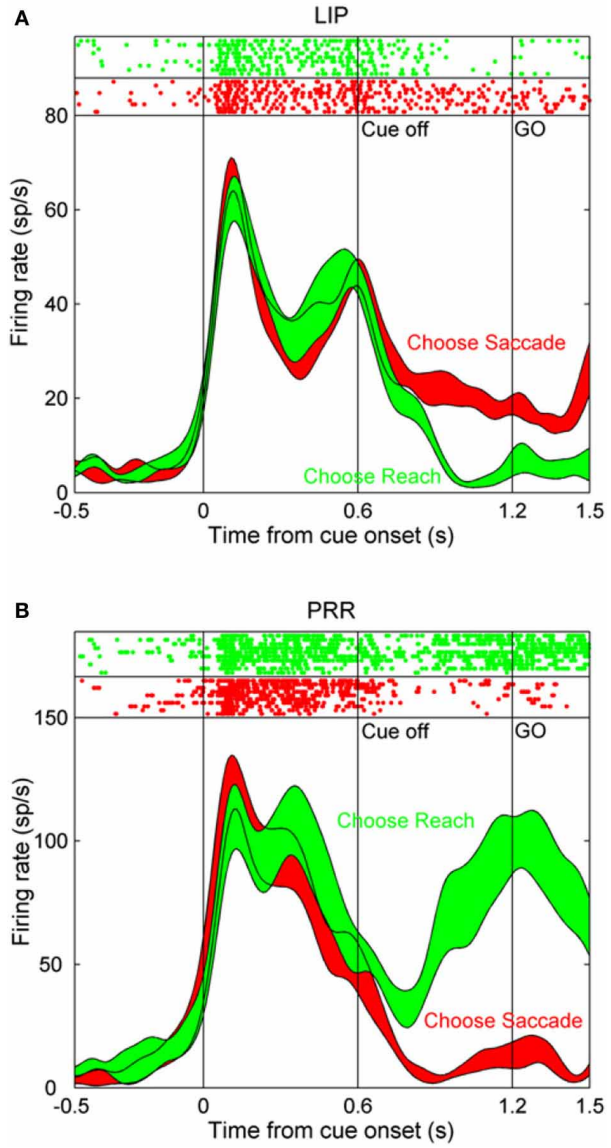

FIGURE 1 | The activity of single neurons in the lateral intraparietal (LIP) area and in the parietal reach region (PRR) during a task in which monkeys autonomously decided to make a saccade or a reach toward the same remembered visual target location. (A) After the initial visual transient at the onset of the peripheral cue, activity in this LIP neuron is greater during the following delay period on trials that the monkey decided to make an eye movement (red trace) than an arm movement (green trace). **(B)** Corresponding data in a PRR neuron. Activity in this case was greater on trials that the monkey decided to make an arm movement relative to a saccade. Reprinted with permission (Cui and Andersen, 2007).

controls saccadic eye movements), as the effector specificity of LIP activity appears to suggest, then the distinction between these alternatives becomes difficult to precisely define.

Although the above evidence indicates that neural activity in area LIP relates to the direction of upcoming saccades, by the same token, a substantial body of evidence indicates that saccade control by itself cannot entirely explain the neural representation of space in this area. Neurons in area LIP exhibit short-latency ON responses that are tightly coupled to the appearance of visual stimuli (Bisley et al., 2004), and respond to visual stimuli even in the case that they do not serve as saccade targets (Colby et al., 1996; Platt and Glimcher, 1997; Powell and Goldberg, 2000; Gottlieb et al., 2005; Premereur et al., 2011). By comparing activity of LIP neurons when saccades are made toward and away from visual targets (anti-saccades), it is possible to determine whether the spatial selectivity of neurons is related to the position of the visual stimulus or the direction of the forthcoming eye movement. Under these circumstances, the activity of most LIP neurons reflects the position of the visual stimulus serving as the saccade target and not the direction of the pending saccade (Gottlieb and Goldberg, 1999), although there is some evidence that an initially stimulus-bound spatial signal in LIP converts to a more closely saccade-bound signal as the delay period progresses, and the time of the pending saccade approaches (Zhang and Barash, 2004; Gottlieb et al., 2005). All of these observations indicate the presence of a visual representation in area LIP that does not bear an obligatory relation to the direction of saccades. In fact, LIP neurons can show selectivity for the shape of visual stimuli (Sereno and Maunsell, 1998; Lehky and Sereno, 2007; Janssen et al., 2008), a type of visual feature selectivity that shows a role for LIP in visual processing that extends beyond saccade control.

Although the precise balance of sensory and motor processing in area LIP (and in parietal cortex in general) remains to be determined, there seems little doubt, given that both factors influence activity in posterior parietal cortex, that this area is intrinsically sensorimotor cortex and, as a result, its function is not entirely reducible to one side of this continuum (sensory or motor) considered in isolation of the other. Additional evidence (reviewed below), argues that these same parietal areas are able to also participate in cognitive processes that to various degrees are abstracted from sensorimotor control.

SECOND ORDER SPATIAL CODING: COGNITION AS MODULATION OF THE TIMING AND STRENGTH OF SENSORIMOTOR SIGNALS

A brain confined to processing current sensory input and motor output would be of limited intelligence. Human mental activity, and its contribution to intelligent behavior, depends directly on the capability of cortical systems to represent and process information that is decoupled from sensorimotor control, both in time and in information content. In this section, we consider how relatively simple modifications of sensory and motor signals in posterior parietal cortex can implement a diverse set of sophisticated cognitive processes, including spatial attention, spatial working memory, and decision-processing. The neural correlates of each of these cognitive processes can be understood to emerge by a modification of either the strength or timing of sensory and motor signals in the brain. In each case however, the spatial information coded by neural activity remains tightly coupled to specific stimuli or movements.

Spatial working memory

The spatial delayed response task, which requires monkeys to direct a motor response toward a cue or stimulus that was seen in the recent past (but is not visible at the time of the motor

response) is a classical test of spatial working memory in monkeys (Goldman-Rakic, 1988, 1995). An oculomotor variant of this task (Funahashi et al., 1989), the memory-guided saccade task, requires monkeys to make memory-guided saccades toward the location of a brief visual target several seconds after it has disappeared. During the performance of memory-guided saccades, neurons in parietal area LIP are tonically activated for the interval of time between the presentation of the visual stimulus and the subsequent delayed saccade (Gnadt and Andersen, 1988; Chafee and Goldman-Rakic, 1998). This neural activity appears to play a role in spatial working memory, in the sense that it spans the delay period between stimulus and response and is selective for the spatial information needed to direct that response. Other groups have shown that area 7a contributes to sensory-based spatial working memory (Constantinidis and Steinmetz, 1996; Qi et al., 2010; Rawley and Constantinidis, 2010). Delay activity in parietal cortex observed on spatial working memory remains tightly coupled to stimulus position or movement direction (identifying it as a correlate of a first order spatial cognitive process by the definition above). Only the timing of neural activation with respect to external sensorimotor events has changed.

Spatial attention

Much of the history of posterior parietal research over the last 35 years has been defined by the intention-attention debate, the question as to whether the primary function of this cortical area is to formulate motor plans (Mountcastle et al., 1975; Snyder et al., 1998a, 2000; Quian Quiroga et al., 2006) or to allocate spatial attention (Robinson et al., 1978; Bushnell et al., 1981; Gottlieb et al., 1998; Bisley and Goldberg, 2003, 2006). The two alternatives have proven to be extremely difficult to dissociate experimentally. One reason is that the motor function of parietal neurons in monkeys has often been studied by having monkeys make movements toward visual targets, which suddenly appear at unpredictable locations, and as such are likely to draw bottom-up attention to the stimulus. In addition, spatial attention and motor planning may be functionally linked (Hoffman and Subramaniam, 1995; Deubel and Schneider, 1996), a view articulated by the premotor theory of attention (Rizzolatti et al., 1987). A role for parietal cortex in spatial attention is clearly indicated by the observation that patients with parietal lesions exhibit spatial neglect, a condition in which they fail to consciously perceive stimuli delivered contralateral to their damaged cortical hemisphere (Husain and Nachev, 2007; Corbetta and Shulman, 2011).

Recordings in area 7a have provided evidence that neural activity in this area generates signals that specify where attention should move. The visual responses of 7a neurons are suppressed if attention is already located at the cells' visual receptive field when the stimulus appears, but are robust if attention is directed elsewhere, a finding which could indicate that 7a neurons are activated when the location of attention is shifted (Steinmetz et al., 1994; Robinson et al., 1995; Constantinidis and Steinmetz, 2001b). A similar mechanism could account for the observation that 7a neurons are activated to encode the location of salient stimuli that pop-out form other stimuli in a visual array by virtue of being visually distinct, and therefore drawing attention (Constantinidis and Steinmetz, 2001a, 2005). However, the relation between attention and neural activity in area 7a is complex, and dependent on training. For example, in monkeys trained to base their responses on the position of a stimulus defined in an external frame of reference (rather than the retinal location of the stimulus), neural responses at attended locations are enhanced rather than suppressed (Rawley and Constantinidis, 2010). These data indicate that the relation of neural activity to attention in area 7a is plastic and could reflect the spatial coordinate system the brain has been trained to employ (Chafee et al., 2007), however the nature of task effects on attention-related activity in area 7a is not yet fully understood.

In area LIP, neurons are activated by visual stimuli that appear abruptly in their visual receptive fields even in the case that monkeys never make a saccade toward the stimulus (Gottlieb et al., 1998; Kusunoki et al., 2000). Moreover, it appears that the abrupt onset of the stimulus, and the potential capture of bottom-up attention, accounts for a large part of the neural response, as LIP neurons do not respond to the presence of identical stimuli brought into their receptive fields by a saccade (Gottlieb et al., 1998; Kusunoki et al., 2000). The activity of LIP neurons is reduced before saccades made without a visual target, and is augmented if the visual stimulus is their receptive field is made task-relevant (Gottlieb et al., 1998; Kusunoki et al., 2000). Subsequent studies have shown that LIP neurons respond briskly to visual events in their receptive fields that grab attention but have no other behavioral significance in terms of instructing a required motor response (Balan and Gottlieb, 2006). **Figure 2**, taken from (Balan and Gottlieb, 2006), illustrates this effect in LIP neurons studied during a covert visual search task. Population activity functions plot the increase in firing rate of LIP neurons when the stimulus in their visual receptive was briefly perturbed (for example by shifting color or changing position slightly). Each of these visual events had no bearing on the type or direction of the required motor response, yet each produced an increase in the activity of LIP neurons. These data provide evidence that LIP neurons can be driven by visually salient stimuli, regardless of their motor significance. Conversely, the responses of LIP neurons to visual stimuli are suppressed if those stimuli are overtly ignored (Ipata et al., 2006). These and other data support the view that area LIP generates a salience map of visual space (Goldberg et al., 2006; Gottlieb, 2007).

To directly examine whether neural activity in LIP observed during motor planning tasks may reflect the location of spatial attention, Bisley and Goldberg presented a probe stimulus in the middle of a memory-guided saccade trial, finding that attention was located at the position of the saccade target, which was the location coded by the concurrently active population of LIP neurons (Bisley and Goldberg, 2003). These authors also found that the tight correspondence between the location of spatial attention and the location coded by neural activity in area LIP persisted when attention was transiently drawn to a distractor stimulus, even though this never served as the target for a movement (Bisley and Goldberg, 2003).

Collectively, these data provide strong evidence that neural activity in area LIP has a role in visual attention that can, with experimental care, be dissociated from motor planning. However, the data do not seem to preclude that neural activity in LIP

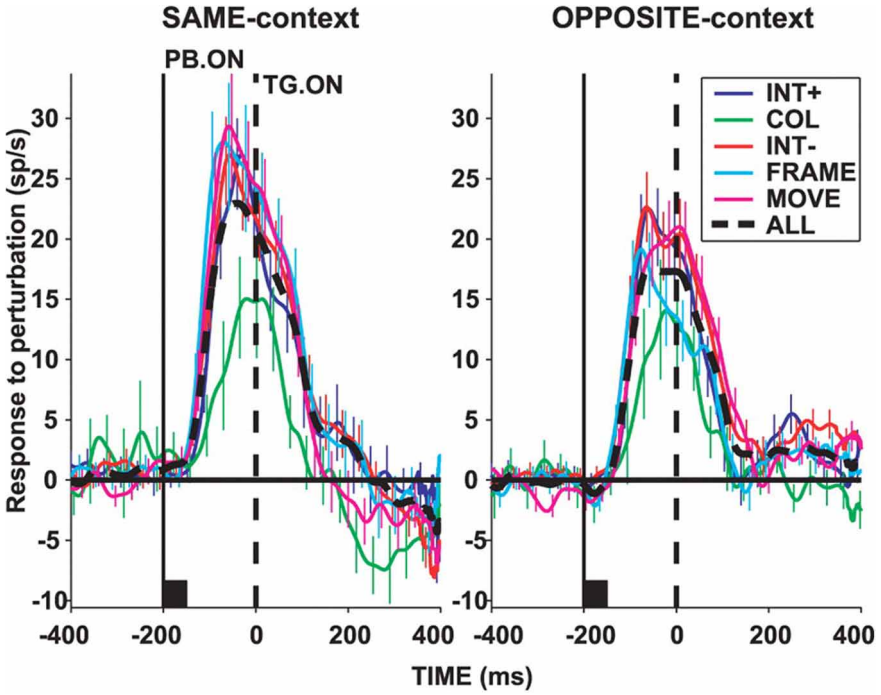

FIGURE 2 | Population activity in area LIP of monkeys performing a covert visual search task using a stable stimulus array. Activity functions plot the difference in mean LIP neuronal population firing rate when the stimulus in the receptive field (RF) underwent a salient perturbation vs. when it did not. Upward deflections indicate an increase in firing rate caused by the salient visual event regardless of whether the search target was located inside ("SAME-context"), or outside ("OPPOSITE-context") the receptive field. Visual perturbations included an increase ("INT+"), or decrease ("INT−") in stimulus intensity, a change in color ("COL"), a shift in stimulus position ("MOVE"), or appearance of a bounding frame ("FRAME"). In each case, the visual perturbation was task-irrelevant and had no bearing on response selection. Reprinted with permission (Balan and Gottlieb, 2006).

provides spatial targeting information preferentially to the oculomotor system (via output projections to the frontal eye fields and superior colliculus, for example). It seems likely, given the quantity of evidence on both sides of the debate, that attention and intention colocalize to posterior parietal cortex, and may represent two sides of one coin, in the sense that a spatial bias signal originating in parietal cortex could simultaneously influence processing in motor and sensory areas that receive parietal input (Cavada and Goldman-Rakic, 1989a,b; Andersen et al., 1990a; Wise et al., 1997; Marconi et al., 2001; Tanne-Gariepy et al., 2002) albeit to different degrees depending on task conditions. If the fundamental role of parietal cortex is to derive spatial information from the sensory input and relay this spatial information to motor systems, it would seem advantageous if the spatial representation were selective, restricted to the most salient or behaviorally relevant stimuli, to prevent motor systems from being inundated with more spatial targeting information than they could effectively translate into movement at any given instant.

In all of the above studies, regardless of whether the neural activity observed reflected a motor plan, a map of behavioral salience, or a shift in covert attention, the spatial information coded by that activity related directly to the position of a visual stimulus or the direction of a forthcoming movement. In this regard, spatial attention qualifies as a second order spatial process by the definition above. The neural representation is a joint function of sensorimotor and cognitive factors, but the spatial content of the neural representation maintains a close relationship to stimulus position or movement direction. In these instances, then, spatial cognition rests upon a neural mechanism that is only partially decoupled from sensory processing or sensorimotor control. The neural correlate of spatial attention in this case consists essentially of a variable gain imposed by a cognitive process on a fundamentally sensory signal.

Spatial decision-processing

Neural recordings in posterior parietal cortex of monkeys during decision-making tasks have provided crucial insight into the neural mechanisms involved, and in most of these studies, the neural mechanisms of decision-processing have reflected a second order spatial process as defined above. In one widely used paradigm, monkeys make a decision to saccade in a particular direction based the predominant direction of visual motion in a field of moving dots. By systematically varying the proportion of dots moving in the same direction, it is possible to produce motion percepts of graded strength (Newsome et al., 1989). Under these conditions, LIP neurons are more strongly active before saccades in their preferred direction if the decision is based on a stronger motion percept (Shadlen and Newsome, 1996, 2001; Roitman and Shadlen, 2002; Churchland et al., 2008; Kiani and Shadlen, 2009). This provides evidence that LIP activity scales with the confidence or certainty of a spatial decision. Under a control condition in which the dots move in random directions (and there is no

coherent motion percept) monkeys saccade in variable directions. The fact that LIP activity continues to predict saccade direction in this case (Shadlen and Newsome, 1996) makes it difficult to interpret the activity as reflecting visual salience or attention only, as neural activity predicts the variable saccade direction over trials in which the positions of visual targets and the features of the motion stimulus do not vary. Subsequent studies have refined our understanding of the neural mechanisms that mediate the decision, providing evidence that LIP neurons integrate motion information over time (Huk and Shadlen, 2005), and that once activity in LIP reaches a boundary, the saccade is executed (Kiani et al., 2008). In the most widely used version of the moving dot perceptual decision task, the perceived direction of visual motion (the perceptual decision), and the direction of the saccade (the motor decision) are coupled, making it difficult to determine whether neural activity reflected spatial aspects either of the stimulus or the required motor response. In a recent study dissociating these two spatial variables, visual motion and saccade planning directions independently modulated the activity of single LIP neurons (Bennur and Gold, 2011), confirming a role for parietal cortex in both visual and motor processing.

Rather than varying the strength of sensory evidence, other studies of decision-making have systematically varied the magnitude or probability of reward. This approach has successfully demonstrated that increasing reward magnitude or probability enhances the strength of saccade planning activity in LIP (Platt and Glimcher, 1999). Subsequent studies simultaneously manipulating both the strength of sensory evidence and the magnitude of reward have shown that both factors influence motor planning activity in LIP (Rorie et al., 2010). Under real world conditions, decisions are often not dictated by explicit sensory cues, but rather reflect varying estimates of action value based on past decisions and outcomes. Under these conditions, neural activity in LIP reflects a temporally local (and continuously varying) estimate of action value (Sugrue et al., 2004). Neural activity showing this relationship is illustrated in **Figure 3**. In this experiment, the authors derived an estimate of the subjective value that monkeys assigned to alternative actions (the local fractional income) which reflected how much reward monkeys had earned for a given action in the recent past, and that accurately predicted their subsequent choices. Activity functions in **Figure 3** illustrate the firing rate of a population of LIP neurons when their preferred saccade was associated with different values. As the local fractional income of the saccade target increased, the intensity of LIP activity increased also (**Figure 3**; blue activity functions of increasing thickness). These data provide clear evidence that neural activity in LIP reflects not only saccade direction but also the value attributed to the saccade.

Other studies have shown that LIP neurons are involved in aspects of decision-processing that extend beyond the evaluation and neural representation of action value. For example, in monkeys adjusting their response strategy to beat a computer opponent in a free-choice oculomotor game, LIP neurons encode both the current value of alternative actions, as well as actions and outcomes on prior trials, information that could play a role in adjusting strategy to counteract the computer opponent (Seo et al., 2009). Finally, the activity of LIP neurons bears a basic relation to reward prediction, even when the reward is not a consequence of a particular action. For example, neurons in this area emit stronger responses to visual stimuli that signal the delivery of reward relative to stimuli that do not, even when the location of the stimulus does not bear any relation to the direction of the saccadic response (Peck et al., 2009).

Scaling motor plans as a function of value or anticipated reward could be expected to bias the competition among alternative motor plans in favor of the action with the highest payoff.

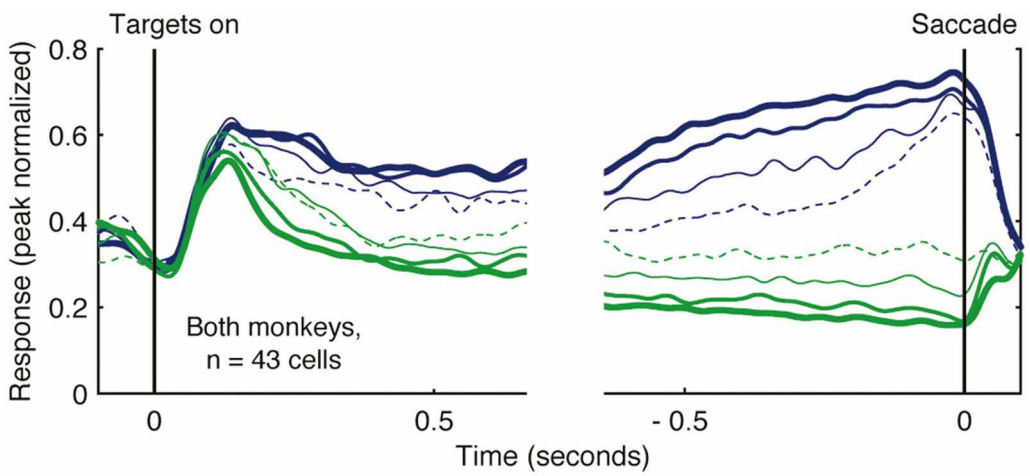

FIGURE 3 | Activity of LIP neurons scales with action value in a decision-making task. Monkeys decided whether to saccade toward one of two alternative targets (red or green) under conditions in which the reward that each target would deliver changed dynamically as a function of choice and reward history. Spike density functions plot the mean firing rate of 43 LIP neurons as a function of the local fractional income, or the proportion of recently earned reward attributed to the color of the saccade target, that the monkey selected. Activity when the monkey decided to saccade toward the target in the receptive field is illustrated in blue, and to the target away from the receptive field in green. Lines of increasing thickness indicate greater fractional income associated with the selected target. Reprinted with permission (Sugrue et al., 2004).

This formulation of decision-processing bears a strong resemblance to the biased competition model of visual attention, in which attention biases the competition between multiple stimulus representations in favor of those which are most salient or behaviorally relevant (Desimone and Duncan, 1995). The finding that expected reward can also modulate visual signals in area LIP (Peck et al., 2009), in addition to motor signals as indicated by the above studies of decision-processing, suggests that visual attention and decision-processing may be mediated by similar neural mechanisms (Gottlieb and Balan, 2010).

From the perspective of spatial sensorimotor independence, the above studies characterize decision-processing as a second order spatial process. The data show that LIP activity that codes the direction of the next saccade is modulated in strength according the predicted outcome or subjective value of an action. However, the influence of reward or value-related cognitive variables on neural activity does not force the spatial representation itself in LIP away from a tight relationship to the spatial aspects of sensory input or motor output. More specifically, the spatial information coded by neural activity in the majority of these studies continues to represent the spatial features of particular visual stimuli (e.g., the position or direction of motion of visual stimuli), or the spatial features of particular movements (e.g., the direction of a planned saccade).

THIRD ORDER SPATIAL PROCESSING: DECOUPLING SPATIAL REPRESENTATION FROM SENSORIMOTOR CONTROL

As indicated by the experimental findings reviewed above, a rich variety of spatial cognitive operations can be achieved by modulating the duration or intensity of neural signals that code stimulus position or movement direction. In this section we will consider the evidence that neural representations of space in posterior parietal cortex can be decoupled from sensory and motor processing to support more abstract forms of spatial cognition. Our interest is to understand how spatial information which is abstracted from sensory or motor processing is represented by the activity of parietal neurons and is utilized to direct spatially intelligent behavior. A rapidly growing body of evidence indicates that posterior parietal neurons participate in a broad range of functions that extends beyond the boundaries of spatial attention or sensorimotor control, to provide neural representations of abstract cognitive variables such as numbers (Nieder and Miller, 2004), rules (Stoet and Snyder, 2004), categories (Freedman and Assad, 2006; Goodwin et al., 2012; Swaminathan and Freedman, 2012), and time (Leon and Shadlen, 2003; Janssen and Shadlen, 2005). Here we will focus on studies providing evidence that the computational capacity of parietal neurons extends to include abstraction in the spatial domain, characterized by neural signals that code spatial information related to the solution of spatial cognitive problems rather than spatial sensorimotor control.

Spatial representation during route traversal

One spatial cognitive task that generates abstract spatial representations in parietal cortex is the traversal of routes. Recent human imaging studies have found that parietal cortex is activated when subjects must navigate through an environment (Shelton and Gabrieli, 2002; Rosenbaum et al., 2004; Wolbers et al., 2004; Spiers and Maguire, 2007; Ciaramelli et al., 2010). This activity is often characterized as reflecting spatial processing in egocentric coordinates. In non-human animals, however, there is evidence to indicate that parietal cortex may process higher-order information during navigation. For example, single neurons in rat parietal cortex have been shown to reflect a "route-centered" reference frame (Nitz, 2006). These cells were activated in a similar manner across different traversals of a particular route, independent of the absolute spatial location or direction of motion. Similar neurons have been recorded from medial parietal areas in monkeys (Sato et al., 2006). These cells varied their activity across movements of the same type in the same place, but which were part of different routes. Further evidence of a non-egocentric representation of space was obtained in experiments in which lesions to area 7a in cynomolgus monkeys resulted in impairments in the traversal of whole-body mazes (Traverse and Latto, 1986; Barrow and Latto, 1996). Monkeys with these lesions had difficulty using information from visual cues to navigate. In one experiment, some monkeys relied on the locations of visual cues to navigate to the exit of the maze, while others learned a series of turns and ran the same route regardless of where in the maze they started. The area 7a lesions only affected those monkeys that used the visual cues to navigate, suggesting that this area is involved in the integration of visual landmarks in navigation.

Spatial representation during covert maze solution

Another realm in which spatial cognition is seen to be decoupled from stimulus and movement parameters is in the solution of visual mazes. Behavioral studies of humans and monkeys following paths in mazes suggest a covert process that analyzes the path, taking a longer time when the path is longer or has more turns in it (Crowe et al., 2000; Chafee et al., 2002). This path-tracking behavior is similar to the following of a route on a map, which is itself a spatial operation related to navigation. Imaging of human subjects who both navigated a 3-D virtual environment and viewed a top-down, or survey, view of the environment showed that many brain areas, including superior parietal cortex, were activated in both tasks (Shelton and Gabrieli, 2002).

Georgopoulos and colleagues (Crowe et al., 2004) recorded from parietal area 7a neurons as monkeys mentally followed a path within a maze displayed on a computer screen (**Figure 4**). During this task, about one quarter of all cells recorded showed activity that was tuned to direction of a straight path emanating from the center of the maze. An example of such a neuron is shown in **Figure 4A**.

This tuned activity was related to the solution of the mazes in a manner that was distinct from sensorimotor parameters. Neurons recorded from a monkey that viewed and attended to maze stimuli, but did not solve them, did not show tuning for path direction. Additionally, data from visual and oculomotor control trials showed a dissociation of neural activity during maze solution and sensory/motor processing. Of the cells that were tuned in the maze task, three quarters were *not* tuned to the direction of eye movements in a delayed saccade task, and the cells that were tuned in both tasks had tuning functions that were not systematically aligned. Maze tuning was similarly dissociated from visual stimuli in control tasks. Few maze-tuned neurons showed tuning

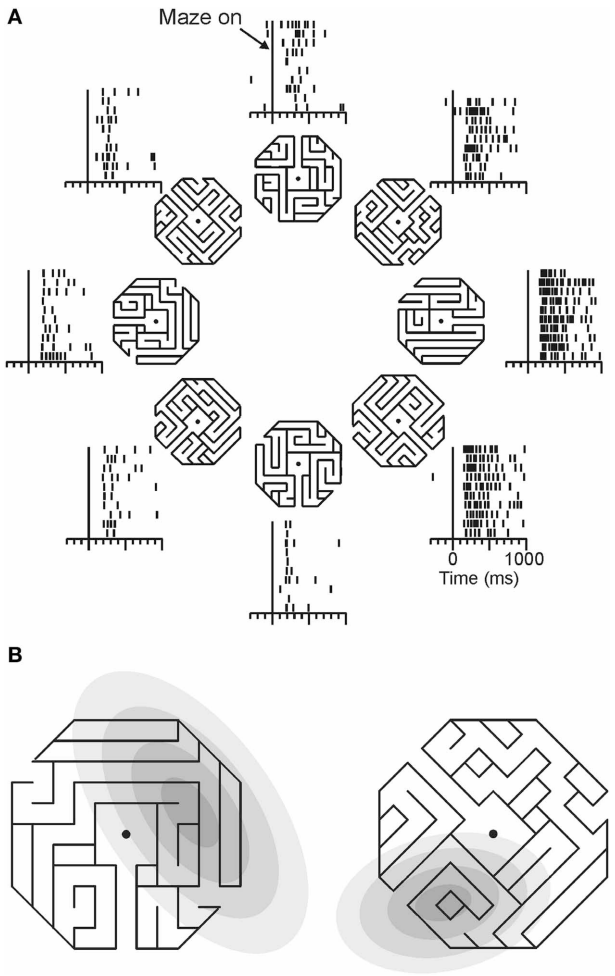

FIGURE 4 | Directional tuning of a parietal neuron during maze solution. (A) One maze stimulus was shown on each trial (mazes were 30° of visual angle across) centered on the gaze fixation target. Monkeys were trained to indicate whether the path that emanated from the center of the maze reached an exit or ended inside the maze. Only straight exit paths are shown in this figure. Each raster shows the neural activity of an area 7a neuron during trials in which the followed path pointed in the indicated direction. **(B)** The direction of the path emanating from the center of each maze indicates the preferred maze path of each cell. Gray ellipses indicate, in the same spatial scale, the locations of each cell's visual receptive field, mapped with focal stimuli. Across the population, there was no concordance between receptive field location and preferred maze path direction.

during the cue period of the delayed saccade task, and locations of independently mapped receptive fields were unrelated to preferred maze directions (**Figure 4B**). Across the population of cells, there was no systematic relation between the location of the visual receptive fields and cells' preferred maze directions, suggesting single neurons could carry independent spatial signals under the two different task contexts.

As a final indication that this neural activity reflected a spatial cognitive process, Crowe and colleagues measured the directional tendency of the neuronal population over time during maze solution (Crowe et al., 2005). In cases when monkeys solved mazes with straight paths, the neuronal population vector (Georgopoulos et al., 1986) began pointing in the direction of the path shortly after the maze was displayed, and remained pointing in that direction over the course of the trial (**Figure 5A**). In trials in which the monkeys solved mazes with a single right-angle turn, the population vector rotated in the direction of the turn (**Figure 5B**). This change in neural activity occurred in the absence of any change in visual stimulation, and in the absence of motor output.

Interestingly, the rotation of the population vector was characterized by the subsequent activation of cells whose preferred directions pointed in the direction of the initial maze direction, and then of cells whose preferred directions pointed toward the maze exit, at an angle of 45° defined with respect to the gaze fixation target. There was no activation of cells with preferred directions 90° from the initial path direction (which would be predicted if the spatial signal in area 7a reflected the direction of movement through a path with a 90° turn). This suggested that the progression of the cognitive process following the path through the maze could be related to the neural representation of a vector with an origin that remained anchored at the fovea, and a tip that moved progressively along the maze path from origin to exit. These results, taken together, highlight the cognitive nature of these spatial signals recorded from parietal cortex, and their dissociation from sensory and motor parameters.

Spatial representation during object construction

Damage to the posterior parietal cortex disrupts spatial cognition, in addition to spatial attention and sensorimotor control. Constructional apraxia provides an example of a spatial cognitive disturbance seen after parietal damage that cannot be explained purely in terms of a sensory or motor deficit. Patients with this syndrome are unable to analyze and effectively reproduce the spatial structure of objects when they attempt to draw or assemble a copy of them. The copies they produce are spatially disorganized—parts are omitted and the ones included are frequently placed in the wrong positions relative to one another, so that the constructed object is disarrayed. These spatial deficits can be observed in patients that do not otherwise exhibit frank visual or motor impairments (Piercy et al., 1960; Benton and Fogel, 1962; Benton, 1967; Benson and Barton, 1970; Arena and Gainotti, 1978), suggesting a specific deficit in spatial cognition. The cognitive deficit underlying constructional impairment could reflect a reduced ability to compute task-critical spatial relationships, in that the spatial structure of an object is specified by the set of spatial relationships that locate its parts with respect to one another. As a set, these spatial relationships provide a view-invariant representation of object structure that generalizes across different object positions or orientations, and it seems likely that to facilitate operations on objects, the brain generates spatial representations of this type (Olson, 2003). Prior studies have shown that neurons in the supplementary eye fields code saccade direction in object-centered coordinates (Olson and Gettner, 1995, 1999; Olson and Tremblay, 2000; Tremblay et al., 2002; Olson, 2003; Moorman and Olson, 2007a,b). However, the existence of object-centered spatial coding in parietal cortex has been debated. A prior study examined whether LIP neurons code

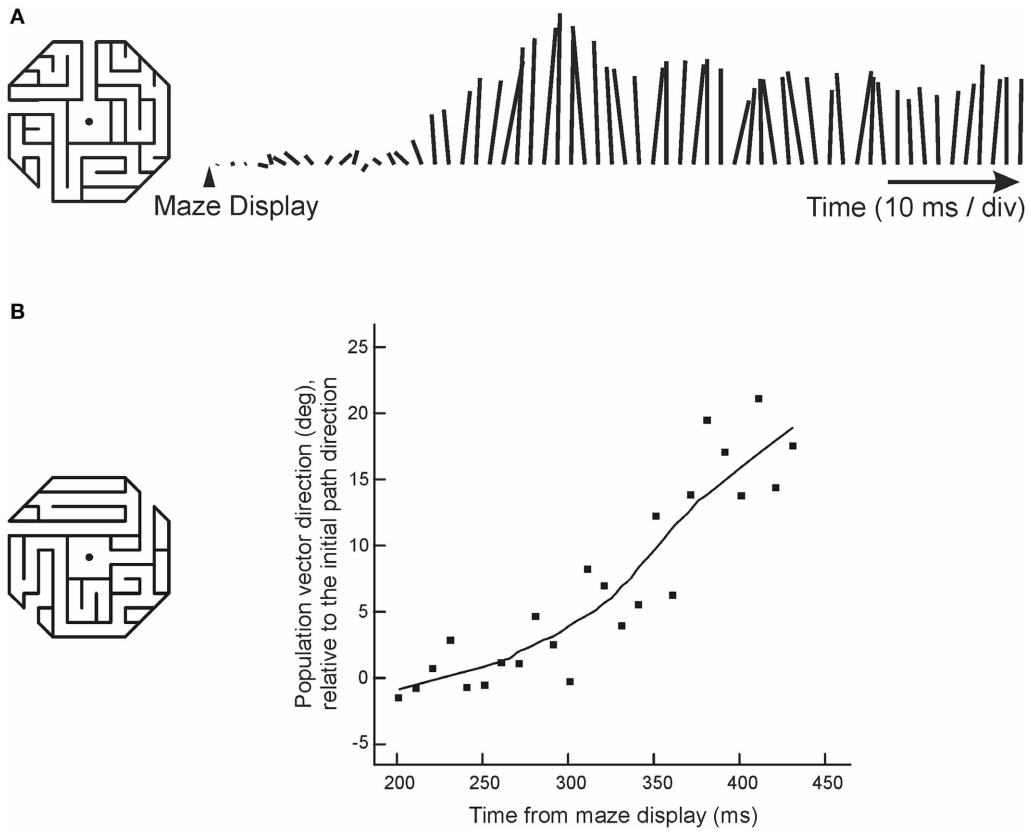

FIGURE 5 | Dynamic neural activity during maze solution. (A) The lines to the right of the maze indicate the length and direction of the population vector, calculated every 10 ms. This example shows the behavior of the population vector during solution of mazes with straight paths that pointed up. The population vector began growing in the direction of the maze by about 200 ms, and continued to point up throughout the trial. **(B)** When monkeys solved mazes with a right-angle turn, the population vector first pointed in the initial path direction and then rotated in the direction that the path turned (positive values in the graph represent angles in the direction the path turned, negative values represent angles away from the turn).

saccade direction in object-centered coordinates and reported largely negative results (Sabes et al., 2002). Further, although parietal lesions cause object-centered spatial neglect (Driver et al., 1994; Tipper and Behrmann, 1996), the loss of fundamentally retina-centered spatial representations could theoretically explain this deficit (Driver and Pouget, 2000).

To study the neural correlates of cognitive operations involved in the analysis of the spatial structure of objects, and to determine if parietal neurons might support object-centered representations of space, Georgopoulos and colleagues trained monkeys to perform an object construction task based on human clinical tests of constructional ability and recorded neural activity in posterior parietal area 7a during task performance (Chafee et al., 2005). The sequence of task events is represented at the top of **Figure 6**. Monkeys were presented with two objects each trial consisting of an arrangement of squares. The first object was the model that monkeys were required to copy. The second object was a partial copy of the model, identical except that one square was missing. Monkeys had to compare the structure of model and copy objects to locate the missing square in the copy object. They then replaced the missing square to reproduce the model configuration for reward. (Monkeys selected one of two sequentially presented choice squares by timing when they pressed a single response key, so movement direction did not vary over trials.)

Neural activity in area 7a varied systematically as a function of the missing square in the copy object. This provided an example of a case in which parietal activity coded a cognitive spatial variable rather than a sensorimotor one because the task was designed so that the location of the missing square did not correlate either with the retinal position of a visual stimulus or the direction of the required motor response. Rasters (**Figures 6A–L**) illustrate a single area 7a neuron that was activated during the copy period of the task (shaded vertical gray rectangle), but only on the subset of trials in which the configurations of the model and copy objects, taken together, jointly localized the missing square to the lower left position within the copy object. The spatial information coded by this neural activity did not derive directly from the visual features of the objects (such as position or configuration). For example, the trials illustrated across the top row (**Figures 6A–D**) all presented the same copy object at the same position in the visual display, but neural activity clearly varied as a function of where the monkey had determined the missing square was located on each trial. Examination of the pattern of activity across trial conditions demonstrates that activity in this

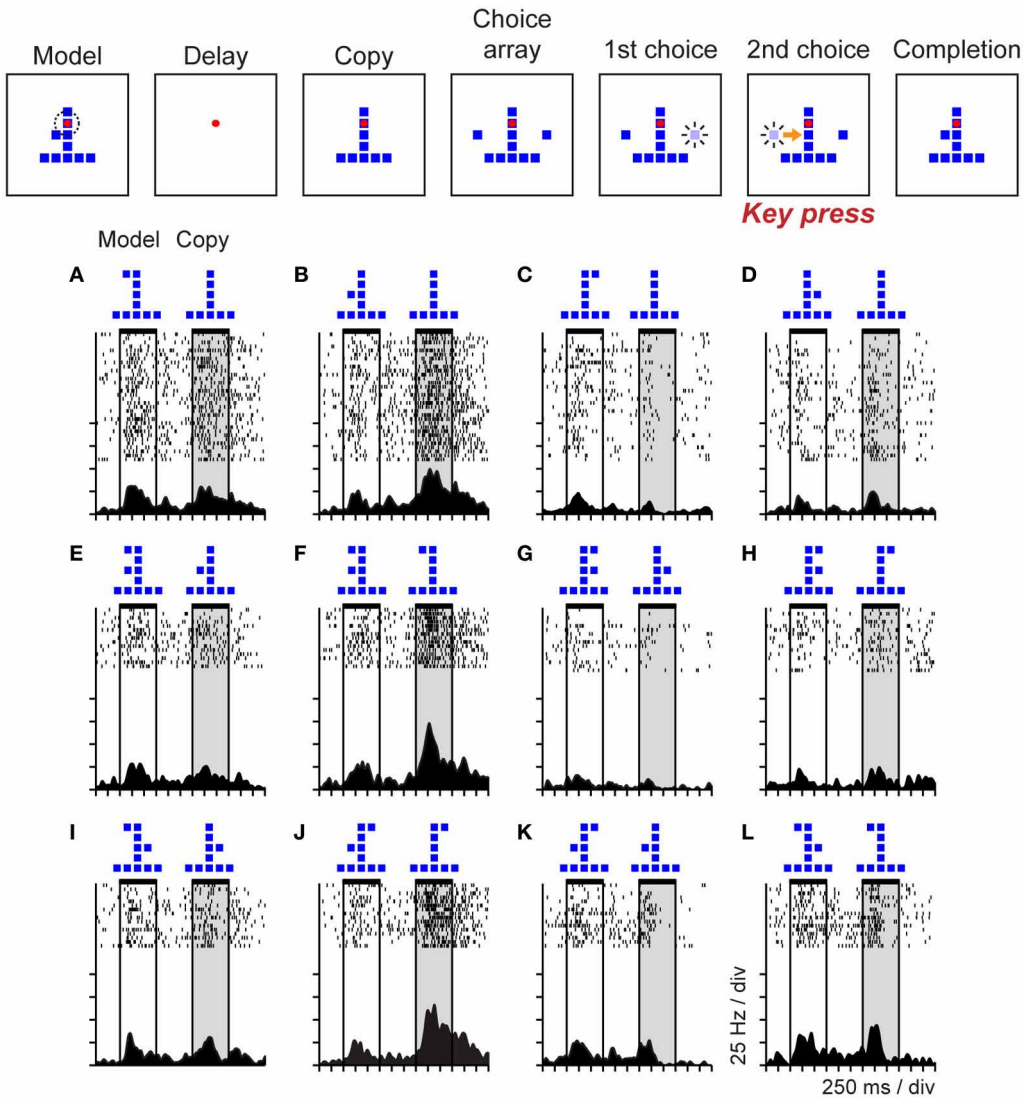

FIGURE 6 | Event sequence of the object construction task and activity of a single neuron in area 7a during task performance. Stimuli displayed during the trial are shown in the top panel. Monkeys viewed a model followed by a copy object (each consisting of an arrangement of squares). The copy was identical to the preceding model except that a single square was missing. Monkeys had to localize the missing square and replace it to reproduce the model configuration for reward. Addition of a square to the copy was via a forced choice. Two choice squares were presented and brightened in random sequence. The monkey controlled which square was added by timing when it pressed a single response key in relation to the choice sequence (the computer added the square that was bright at the time of response to the copy object automatically). **(A–L)** The duration of model and copy periods is delimited by horizontal black bars at the top of each raster. This neuron was activated primarily during the copy period, on trials in which the model and copy objects presented jointly localized the single square missing from the copy object (relative to the preceding model) to the middle left position within the object.

neuron was not an obligatory function of the configuration of the model object shown earlier in the trial either. Nor did the spatial information carried by the activity of this neuron bear a systematic relation to the direction of motor output (which did not vary over trials). The activity of this neuron therefore appeared to reflect a process more akin to spatial problem solving, than spatial vision or sensorimotor control. The interpretation of this activity as reflecting a cognitive analysis of object structure, rather than a more basic spatial sensorimotor or attention process, is supported by the observation that this neural population was generally not activated when monkeys viewed, planned saccades, or directed attention toward visual stimuli placed at the same locations the cells preferred in the construction task (Chafee et al., 2005). The minority of neurons active during both construction and control tasks often exhibited different spatial tuning in the two contexts, a pattern we had seen during visual maze solution (**Figure 4B**) (Crowe et al., 2004).

To explore whether neurons in area 7a might code the location of the missing square during the construction task in object-centered coordinates, we randomly shifted the position of the copy object to the left and right of the gaze fixation target (which defined the center of viewer-centered spatial frameworks), and

found that a large proportion of parietal neurons were insensitive to this manipulation, coding the position of the missing square relative to the object midline in an apparently view-independent manner (Chafee et al., 2007). For example, the neuron illustrated in **Figure 7** was activated when the missing square was located on the relative right (**Figures 7B,D**) and not the left (**Figures 7A,C**) side of the copy object, regardless of whether the copy object itself was presented in the left (**Figures 7A,B**) or right (**Figures 7C,D**) side of viewer-centered space. We did find that the activity of these neurons correlated with the location of covert spatial attention, as monkeys were faster to detect probe stimuli presented unpredictably at the location of the missing square in the middle of a construction trial (Chafee et al., 2007), much the same way that LIP neurons were found to signal the location of attention during the performance of a memory-guided saccade task (Bisley and Goldberg, 2003). However, the 7a neurons we studied during object construction were not generically related to spatial attention, as they failed to activate when monkeys directed attention to the same locations in different task contexts (Chafee et al., 2005). Finally, most of the neurons studied during construction preferred locations on the contralateral side of objects irrespective of the absolute locations of the objects (Chafee et al., 2007). That contralateral bias at the neural population level could potentially explain why object-centered neglect after unilateral parietal damage typically involves the contralesional side of objects (Olson, 2003).

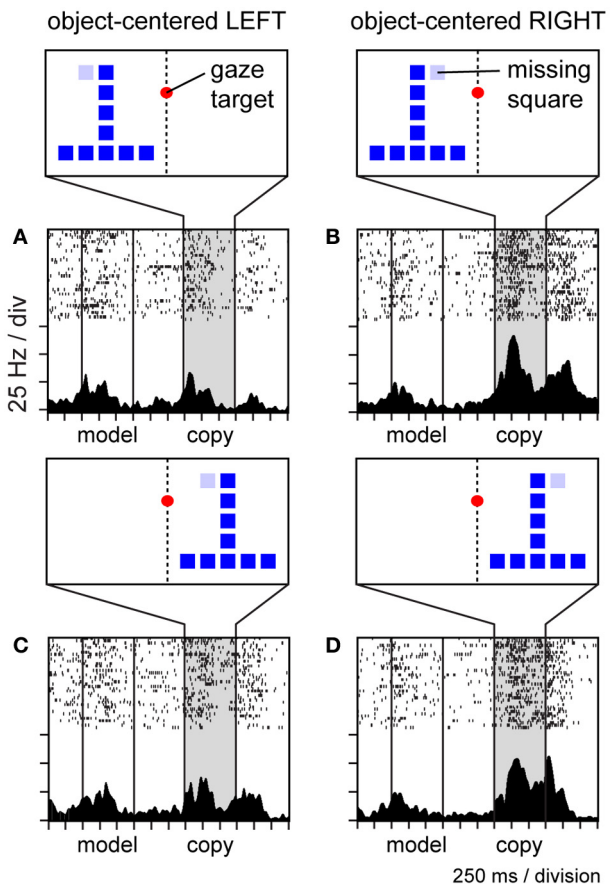

FIGURE 7 | Activity of a single area 7a neuron coding the location of the missing square in the copy object in object-centered spatial coordinates. The location of the missing square is indicated in light blue but was not visible to the monkey (the copy object consisted only of an inverted "T" configuration of dark blue squares in these trials). The copy object was presented to the left **(A,B)** or right **(C,D)** of the gaze fixation target at random over trials. The missing square was located on the relative left **(A,C)** or right **(B,D)** side of the object, relative to its intrinsic midline, at random over trials. Consequently, the object-centered and viewer-centered side (left or right) of the missing square in the copy object were statistically independent spatial variables. This neuron was activated whenever the missing square was located on the relative right side of the copy object **(B,D)**, regardless of whether the copy object appeared in left **(B)** or right **(D)** viewer-centered space.

Representation of spatial categories

Object-centered spatial codes provide an example of how neurons can carry spatial information that generalizes across a potentially infinite set of specific stimulus conditions, so long as the defining abstract feature, the spatial relationship (between a point in space and an object) holds. Spatial categories (categories defined on the basis of spatial information) are analogous in that they similarly exemplify spatial regularities or underlying principles that can be embedded in a potentially infinite set of different stimulus configurations, and prior work has shown that parietal neurons code spatial categories. For example, posterior parietal neurons code categories of visual motion direction (Freedman and Assad, 2006; Swaminathan and Freedman, 2012) and spatial position (Merchant et al., 2011) in a dichotomous fashion when these continuously varying stimulus attributes cross a learned or inferred category boundary. The finding that parietal neurons coded object-centered position (**Figure 7**) suggested they might also code spatial categories based on spatial relationships. To explore that possibility, monkeys were trained to place a spot visual stimulus into a spatial category on the basis of its spatial relationship to a line serving as a category boundary. Stimuli were presented in a circular array, and the category boundary bisected the array in either a vertical or horizontal orientation (**Figures 8A,B**), instructing either a left/right categorization rule (LR rule), or an above/below categorization rule (AB rule). This placed categorization under executive control. Population activity in parietal area 7a reflected the assignment of positions to categories in a rule-dependent manner (Goodwin et al., 2012). One population of neurons exhibited activity that dissociated left and right categories under the LR (**Figure 8C**) and not the AB (**Figure 8D**) categorization rules. Another population exhibited similar rule-dependent selectivity for vertical categories (**Figures 8E,F**). Activity of this type was dissociated both from the position of the stimulus and the orientation of the boundary, as the rule-dependent category information coded by cells was jointly defined by both factors taken together, and therefore dissociated from either considered individually.

ORIGIN OF THIRD ORDER SPATIAL REPRESENTATIONS

One of the most important questions regarding the hierarchy of spatial representation found in parietal cortex is how neural signals coding abstract spatial information (such as spatial categories or relative positions) derive from simpler sensorimotor signals.

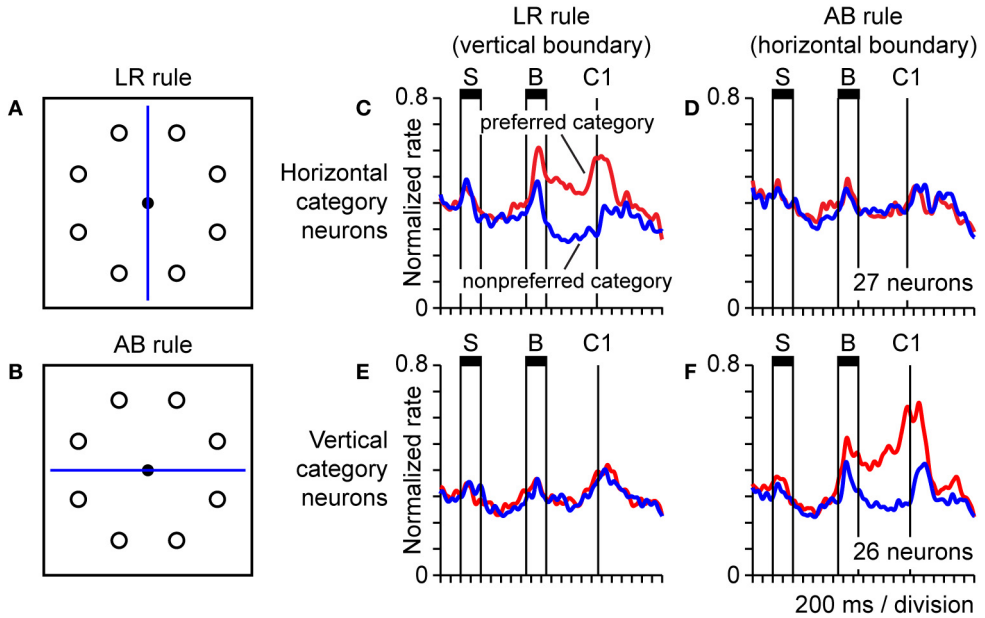

FIGURE 8 | Neural population activity encoding categorical spatial relationships in posterior parietal cortex area 7a. Monkeys performed a task in which they assigned a spot sample stimulus to one of two spatial categories on the basis of the spatial relationship between the sample and a line serving as a category boundary. We presented the sample and category boundary stimuli at different times in the trial, separated by an intervening delay. The durations of the sample and boundary cue are indicated by horizontal bars labeled "S" and "B," respectively **(C–F)**. Monkeys reported their categorical judgment by pressing a response key when a subsequent choice stimulus appeared in the same spatial category as the sample (the time of onset of the first choice is labeled "C1") **(A,B)**. Circular array of sample stimulus positions and category boundary shown bisecting the array in either a vertical or horizontal orientation (the orientation of the boundary varied over trials). A vertical boundary instructed the monkey to divide the circular array of positions into the spatial categories left and right (LR rule). A horizontal boundary instructed the monkey to divide the circular array of positions into the spatial categories above and below (AB rule) **(C,D)**. Activity of a population of 27 parietal neurons coding the horizontal category of the sample under the LR rule **(C)** and not the AB rule **(D)**. Population activity is plotted separately for trials in which the sample fell in the preferred (red) and non-preferred (blue) horizontal category for each neuron, defined on the basis of the position of the sample stimulus **(E,F).** Corresponding data for a distinct population of 26 area 7a neurons coding the vertical categories above and below under the AB rule **(F)** and not the LR rule **(E)**.

The answer should provide insight, perhaps of general scope, into how neural systems acquire the capacity for abstraction as a function of sensorimotor experience. In the practical context of most neurophysiological experiments, this amounts to understanding how abstract neural signals in the brain emerge as a function of training to perform a particular behavioral paradigm. Cognitive paradigms developed for monkeys are generally of a relatively simple form; however they capture something fundamental to more elaborate forms of cognition in humans. The brain has to generate a set of cognitive representations that capture an implicit principle of general applicability embedded in a set of superficially disparate stimuli or events. Neural signals coding spatial categories provide one concrete example (**Figure 8**). The grouping criteria governing category membership, based on a spatial relationship in this case, is the generalized principle, which could be applied to categorize a potentially infinite set of exemplars. Once these abstract representations emerge, the brain then has to discover the correct mappings between sensory input, cognitive signals, and motor commands.

We know comparatively little about the neural mechanisms by which repeated experience with the world leads to the emergence of cognitive neural signals in the cortex, and the capacity for abstraction and prediction in novel circumstances that these signals are likely to underlie. However, there is little doubt that reward processing and reward-modulated synaptic plasticity play an essential role, although the role of training may differ for second and third order processes as defined above. For example, there is interesting evidence that signals that reflect working memory (a second order process) in prefrontal cortex are present in experimentally naïve animals before training (Meyer et al., 2007), although the information encoded by this activity increases with training (Meyers et al., 2012). That suggests that there exists, to a certain degree, a native working memory capability continually operating in the background to effectively buffer the sensory input regardless of its learned behavioral significance. However, it seems equally like that most of the third order cognitive signals described, such as those coding abstract categories of experimental stimuli, or rules governing task contingencies, did not pre-exist in the cortex of monkeys prior to training. In fact there is evidence that training exerts a powerful effect on category-selective neural signals both in parietal (Freedman and Assad, 2006) and prefrontal (Freedman et al., 2001; Cromer et al., 2010; Roy et al., 2010) cortex. To our view, the fact that most third order spatial cognitive signals so far described are likely to be "trained into" the brain does not undercut the utility of this general experimental approach

for studying the neural origins of abstraction at the single cell level. We would argue that similar processes are taking place in the human brain continuously, given that it is likely we learn much of our abstract knowledge by interacting with a statistically structured environment (Tenenbaum et al., 2011), coupled with reward history. Behavioral paradigms used to study neural correlates of cognition in monkeys are formalizations of these same features. To enable abstraction, neurons at higher levels of the cortical processing hierarchy have to detect and extract statistical regularities (perhaps relating to generalized principles or "knowledge") embedded in activity at lower levels, a process that can be effectively modeled in the non-human primate. We know that this process takes place, but how is one of the most important unanswered question presently confronting cognitive neuroscience.

The integration of statistical models of human cognition (Tenenbaum et al., 2011), with theory-informed biological experiments is likely to lead discovery of the neural mechanisms that generate a capacity for abstraction in neural systems. From that perspective, biological data that can test predictions based on theory will be particularly important. Many models of human cognitive processes can be probed to make predictions about how information should flow between populations of neurons that encode different types of behavioral or cognitive information, as sensory inputs are transformed into more abstract cognitive signals to control behavior, for example. We sought evidence of this type of communication between simultaneously active neural populations coding different types of information in posterior parietal cortex. More specifically, we measured short-term fluctuations in the amount of information about a spatial location coded by two different populations of neurons that were coactive in parietal cortex during the object construction task. The first population coded the position of object squares in a retinocentric, or viewer-centered framework, and therefore provided an example of a first order spatial representation. The second population coded the position of object squares in object-centered coordinates. Because object-centered positions are intrinsically relational (and abstracted from specific absolute positions), signals coding them constitute an example of a third order spatial process. To measure interactions between groups of neurons coding these two types of spatial information, we first measured the firing rates of ensembles of neurons coding position in viewer-centered and object-centered coordinates that we had recorded simultaneously, and applied a pattern classification analysis to these firing rates to quantify short-term fluctuations in the strength of the signals coding space in the two coordinate frames. We then employed Granger causality analysis to examine the temporal correlation between the two time series (after accounting for their autocorrelation). Using this approach it was possible to determine that fluctuations in the strength of the viewer-centered signal preceded and predicted variation in the object-centered signal, but not the converse, and only in the case that the groups of neurons representing the two types of spatial information were recorded simultaneously (Crowe et al., 2008). That provided physiological evidence that abstract neural representations at higher levels of the cortical processing hierarchy receive input and derive from signals at lower levels. We also found that viewer- and object-centered representations of space exhibited markedly different population dynamics. Viewer-centered position was represented by a pattern of population activity that was relatively stable over time, whereas object-centered position was represented by a pattern of population activity that was continuously evolving and highly dynamic, such that subsets of cells carrying the same spatial information were briefly activated in rapid and repeatable sequence throughout the trial (Crowe et al., 2010). These data suggest that distinct neural mechanisms are employed to represent spatial information at different levels of the hierarchy in parietal cortex.

It is important to note that parietal neurons encode non-spatial cognitive variables as well, and non-spatial information can coexist with spatial sensorimotor information in the activity of single neurons (Gottlieb and Snyder, 2010). For example, individual LIP neurons can encode both task rules and movement direction (Stoet and Snyder, 2004), or can carry signals that reflect task context and stimulus position (Balan and Gottlieb, 2006), often at different times in a single trial. This combination of signals in LIP neurons may bias the neural representation of space to reflect cognitive factors or represent an intermediate step toward the generation of purely cognitive signals. However, interestingly, inactivation of LIP neurons appears to impair behavior primarily by interfering with spatial selection, leaving the ability to modulate behavior according to non-spatial cognitive factors relatively intact (Balan and Gottlieb, 2009). That suggests that neural signals in LIP encoding non-spatial cognitive factors may reflect top-down input from other cortical structures.

The data reviewed above provides evidence that neural representations of space that exhibit sensorimotor independence in posterior parietal cortex (1) are mediated by context-sensitive signals distinct from those coding stimulus or motor parameters, (2) still bear a relation to spatial attention (but not in a way dictated directly by sensory input), (3) may emerge by virtue of a transformation applied to population activity coding stimuli and movements, and (4) appear to be mediated by population activity that exhibits unique temporal dynamics.

SUMMARY AND CONCLUSION

Perhaps the single most fundamental fact to emerge from the experimental evidence reviewed above is that posterior parietal cortex sustains a hierarchy of spatial representations, which exhibit different relations to behavior and appear to be mediated by distinct neural mechanisms. One of the key dimensions differentiating the levels of this representational hierarchy is sensorimotor independence, the degree to which spatial information coded by parietal neurons remains tightly coupled to stimulus and motor parameters, vs. the degree to which spatial representations diverge from sensorimotor factors to mediate various forms of spatial reasoning or problem solving that could be considered to constitute instances of spatial intelligence. The long-standing debate as to whether spatial signals carried by parietal neurons reflect stimuli vs. movements, or visual attention vs. motor intention, has produced compelling evidence in favor of both conclusions, suggesting that these are not mutually exclusive.

Even in the more abstract case that parietal neurons represent spatial locations dictated entirely by cognitive rather than sensorimotor factors, neurons appear to continue to reflect the location of spatial attention. From that perspective, biases in both sensory and motor processing could be considered simultaneous corollaries of spatial information represented in parietal cortex. A critical question remaining is how abstract spatial representations in parietal cortex are learned, or more specifically, what are the neural mechanisms that derive them from lower level spatial sensory and motor representations in this area. That question seems experimentally approachable, and integration of experimental and theoretical work stands to provide substantial insight into the neural mechanisms involved.

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Unique and shared roles of the posterior parietal and dorsolateral prefrontal cortex in cognitive functions

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The dorsolateral prefrontal cortex (PFC) and posterior parietal cortex (PPC) are two parts of a broader brain network involved in the control of cognitive functions such as working-memory, spatial attention, and decision-making. The two areas share many functional properties and exhibit similar patterns of activation during the execution of mental operations. However, neurophysiological experiments in non-human primates have also documented subtle differences, revealing functional specialization within the fronto-parietal network. These differences include the ability of the PFC to influence memory performance, attention allocation, and motor responses to a greater extent, and to resist interference by distracting stimuli. In recent years, distinct cellular and anatomical differences have been identified, offering insights into how functional specialization is achieved. This article reviews the common functions and functional differences between the PFC and PPC, and their underlying mechanisms.

Keywords: monkey, neurophysiology, neuron, principal sulcus, intraparietal sulcus, persistent activity, attention

INTRODUCTION

The prefrontal cortex (PFC) has traditionally been viewed as the brain area associated with higher cognitive operations and executive function (Goldman-Rakic, 1987; Miller and Cohen, 2001). Neurophysiological experiments in non-human primates have been instrumental in uncovering the nature of prefrontal involvement in mental processes by revealing that activity of prefrontal cortical neurons constitutes neural correlates of cognitive functions. Correlates of a wide range of functions have now been identified in the PFC, including working-memory (Fuster and Alexander, 1971; Funahashi et al., 1989), perceptual decisions (Kim and Shadlen, 1999; Barraclough et al., 2004), abstract rules (White and Wise, 1999; Wallis et al., 2001), reward expectation (Leon and Shadlen, 1999), associative learning (Asaad et al., 2000), categories (Freedman et al., 2001; Shima et al., 2007), numerical quantities (Nieder et al., 2002), and planning of sequences of actions (Averbeck et al., 2002; Hoshi and Tanji, 2004; Inoue and Mikami, 2006; Berdyyeva and Olson, 2010).

Although these studies confirm the involvement of the PFC in cognitive functions, in recent years it has also been recognized that other cortical areas manifest equivalent neural correlates during cognitive operations. The posterior parietal cortex (PPC), in particular, is tightly interconnected with the PFC and has been shown to exhibit similar properties in a wide range of paradigms tested in both areas. Neuronal responses in posterior parietal areas (such as areas LIP and 7a) are also known to be activated during spatial working-memory (Gnadt and Andersen, 1988; Quintana and Fuster, 1992; Constantinidis and Steinmetz, 1996; Chafee and Goldman-Rakic, 1998) and to represent neural correlates of decision-making (Shadlen and Newsome, 1996; Yang and Shadlen, 2007), planning (Crowe et al., 2005), reward expectation (Platt and Glimcher, 1999; Sugrue et al., 2004), rules (Stoet and Snyder, 2004), categories (Freedman and Assad, 2006; Swaminathan and Freedman, 2012), associations (Fitzgerald et al., 2011), and numerical quantities (Nieder and Miller, 2004; Roitman et al., 2007). It is clear, therefore, that representation of neural correlates of higher cognitive functions is not the exclusive domain of the PFC and it has become more difficult to identify neurophysiological differences than similarities between the two areas. Elucidating the shared and unique roles of the prefrontal and parietal cortex will provide important insights into the neural mechanisms of higher cognitive functions. In this review, we will focus on the functional specialization of the PFC and PPC in cognitive processes as revealed by neurophysiological experiments in non-human primates, with an emphasis on visual processing.

ANATOMICAL ORGANIZATION

The primate PFC is subdivided into a medial, lateral, and orbital aspect. Here we will focus on the lateral PFC (colored region in **Figures 1A,B**), and the dorsal subdivision of the lateral PFC in particular (the dorsolateral PFC). Two alternative nomenclatures are widely used in the literature. We will adopt the nomenclature of Preuss and Goldman-Rakic (1991) and focus on areas 46 and 8a, including the frontal eye fields (FEF), a part of area 8a extending in the anterior bank of the arcuate sulcus (**Figure 1A**). In the Petrides and Pandya (1994) nomenclature, the region we will be reviewing corresponds to areas 9/46 and 8A.

The primate PPC also consists of several cortical areas (colored region in **Figures 1C,D**). This review will focus on the inferior lobule (posterior to the intraparietal sulcus) and particularly on the lateral intraparietal area (LIP) and area 7a (**Figure 1C**). In the alternative nomenclature of Pandya and Seltzer (1982), this region includes areas PG, Opt, and POa (**Figure 1D**).

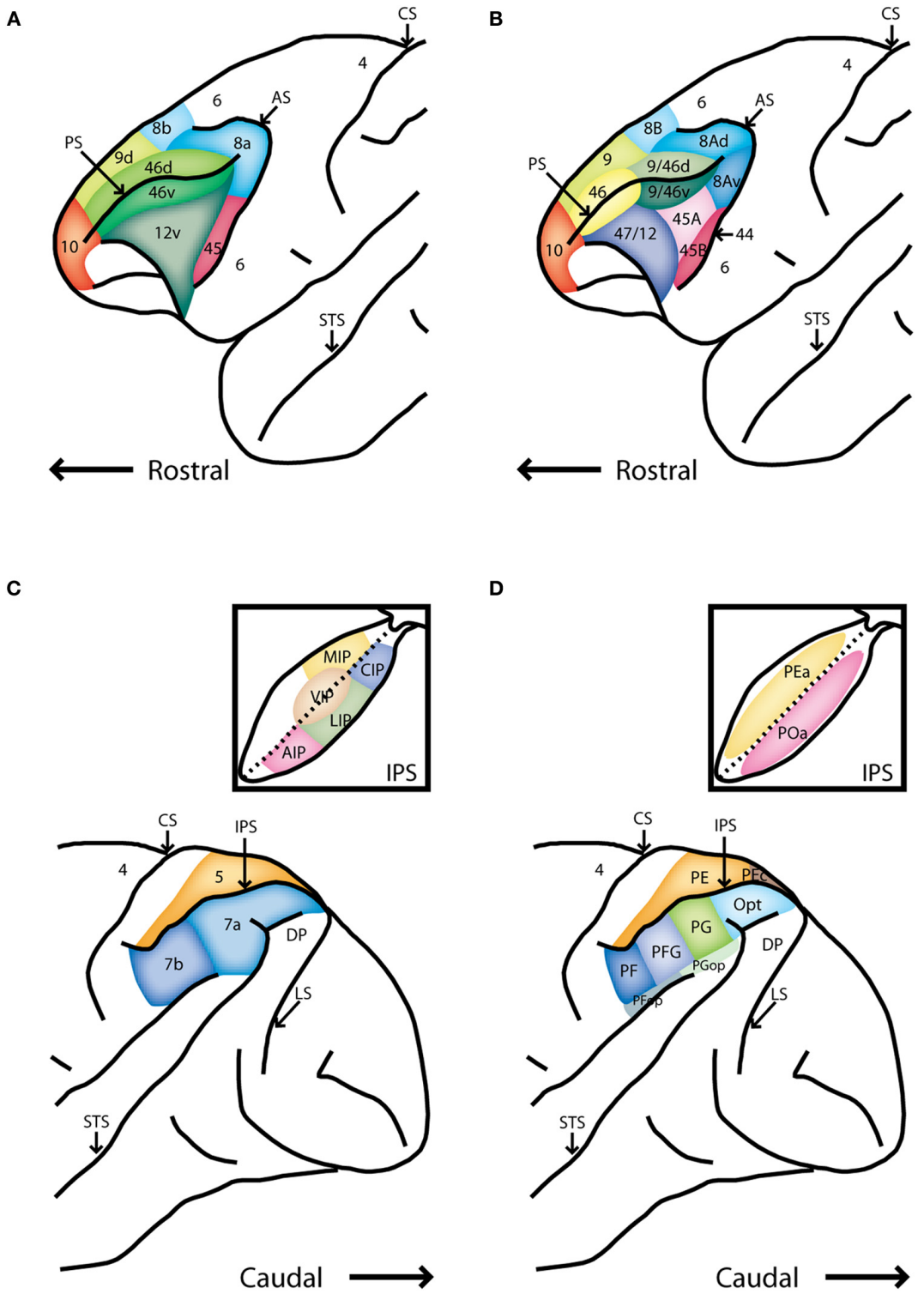

FIGURE 1 | Schematic diagrams of the lateral surface the macaque monkey. (A) Anterior half of monkey brain including the prefrontal cortex, adapted after Preuss and Goldman-Rakic [Preuss and Goldman-Rakic (1991)]. **(B)** Alternative map of prefrontal cortical areas, based on Petrides and Pandya [Petrides and Pandya (1994)]. **(C)** Posterior half of the monkey brain including the posterior parietal cortex. Inset depicts an unfolded view of the intraparietal sulcus Rawley and Constantinidis (2009). **(D)** Map of the posterior parietal cortex based on Pandya and Seltzer [Pandya and Seltzer (1982)]. Abbreviations: AIP, anterior intraparietal area; AS, arcuate sulcus; CIP, caudal intraparietal area; CS, central sulcus; DP, dorsal prelunate area; IPS, intraparietal sulcus; LIP, lateral intraparietal area; LS, lunate sulcus; MIP, medial intraparietal area; PS, principle sulcus; STS, superior temporal sulcus; VIP, ventral intraparietal area.

CORTICAL PATHWAYS

The image of the external world enters the eyes in the form of a continuous stream of light where it is transformed to action potentials in the retina, then transmitted to the lateral geniculate nucleus (LGN) of the thalamus and subsequently relayed to the primary visual cortex. Several dozen visual cortical areas have been identified beyond the striate cortex, organized in a hierarchical fashion (Felleman and van Essen, 1991; van Essen et al., 1992). Two broad pathways with fairly distinct anatomical organization and functional properties are generally referred to as the ventral and dorsal visual streams (Macko et al., 1982; Ungerleider and Mishkin, 1982; Ungerleider and Haxby, 1994). Initially identified based on monkey lesion studies, the ventral stream is traditionally considered as the "what" pathway dealing with representation of stimulus features (such as color and shape); the dorsal stream is described as the "where" pathway and processes spatial aspects of visual information (such as location and direction of motion). Both streams are organized hierarchically with patterns of connections following a stereotypical organization: layer 4 of a cortical area receives input from a subordinate cortical area, transforms the input in layers 2 and 3, and transmits the output to layer 4 of the cortical area to the next stage of the hierarchy (Hubel and Wiesel, 1962, 1965; Douglas and Martin, 2004, 2007). Convergence of inputs at each stage of the cortical hierarchy leads to neurons with progressively larger receptive fields and more complex functional properties. Feedback connections from higher into lower areas follow the opposite pattern: axons originating from layer 5 of the higher area terminate in layers 2 and 3 of the lower one (Felleman and van Essen, 1991; Douglas and Martin, 2004, 2007). In this scheme, the PPC represents the highest stages of the dorsal visual pathway, with area 7a situated at the top level of the hierarchy (Felleman and van Essen, 1991). The PPC in turn projects to the dorsolateral PFC, however, the pattern of axonal termination is not indicative of a clearly hierarchical relationship. The PFC is recognized as a higher order area, yet connections between the two areas are parallel, originating and terminating in the same layers, rather than strictly serial (Barbas and Pandya, 1989; Cavada and Goldman-Rakic, 1989b; Felleman and van Essen, 1991). The relationship of anatomical connections between the two areas, therefore, offers no obvious insight into their relative functional specialization.

INTER-AREAL CONNECTIONS

In addition to dorsal visual stream inputs, the PPC is reciprocally connected with a number of cortical association areas involved in visuo-spatial processing, including the superior temporal, cingulate and parahippocampal cortex, as well as various subcortical structures, including the basal ganglia, pulvinar nucleus of the thalamus, and superior colliculus (Schwartz and Goldman-Rakic, 1984; Selemon and Goldman-Rakic, 1988; Cavada and Goldman-Rakic, 1989a,b). Area LIP, in particular, has direct projections to and from extrastriate visual areas, and other cortical and subcortical areas involved in saccadic eye movements; these include the FEF, basal ganglia, and the superior colliculus, as well as other parietal areas (Asanuma et al., 1985; Lynch et al., 1985; Andersen et al., 1990; Blatt et al., 1990; Stanton et al., 1995). Area 7a is connected with visual cortical areas, including the medial superior temporal area (MST), the parieto-occipital area (PO), and LIP. It is also connected with other cortical association and limbic areas, including area 46 of the PFC, parahippocampal gyrus, and posterior cingulate cortex (Lynch et al., 1985; Selemon and Goldman-Rakic, 1988; Blatt et al., 1990; Rockland and van Hoesen, 1999).

The dorsolateral PFC (areas 8a and 46) processes visuo-spatial information by receiving a direct and robust input from posterior parietal areas 7a and LIP (Selemon and Goldman-Rakic, 1988; Cavada and Goldman-Rakic, 1989b). Area 46 shares many common efferent targets with the PPC, for example the supplementary motor cortex, premotor cortex, superior temporal cortex, cingulate cortex, limbic structures, basal ganglia, thalamus, and the superior colliculus (Selemon and Goldman-Rakic, 1988; Jouve et al., 1998). Area 8a (which includes the FEF) receives visual inputs not only from the PPC but also directly from most extrastriate areas of both dorsal and ventral visual pathways, and the superior colliculus via the thalamus (Huerta et al., 1986; Lynch et al., 1994; Jouve et al., 1998; Sommer and Wurtz, 2002; Ungerleider et al., 2008). Such direct connections with many visual areas allow the FEF to receive diverse and rapid visual input, positioning the area for efficient target selection and gaze shift through effector areas such as the basal ganglia and superior colliculus (Segraves and Goldberg, 1987; Sommer and Wurtz, 1998; Schall, 2002).

FUNCTIONAL ACTIVATION AND SPECIALIZATION

Considering the robust connectivity linking the dorsolateral PFC and PPC and their concurrent activation during a range of cognitive functions, the two brain areas are often viewed as part of a functional unit, the fronto-parietal network (Bisley and Goldberg, 2010). At the same time, a number of functional properties that differentiate the two areas have been discovered or proposed. These can be divided into three broad categories. First, the PFC can be viewed as closer to motor effectors in the cortical circuit generating and executing eye and limb movements. For example, low level ($<50\,\mu A$) microstimulation of the FEF generates saccades (Bruce et al., 1985), while a greater current amplitude is necessary in area LIP for the generating eye movements, which also appear with longer latency (Shibutani et al., 1984). Conversely, motor plans for limb movements have been shown to appear earlier in the parietal lobe (the Parietal Reach Region) than the frontal lobe (Snyder et al., 1997; Cui and Andersen, 2007). In this sense, the fundamental difference between the two areas lies not in the representation of cognitive processes, but in the generation of motor plans dictated by the cognitive factors represented in neuronal activity in both areas. A second view posits that the PFC, due to its intrinsic organization which places parietal and temporal inputs in relative proximity to each other, has the capacity to integrate spatial and feature information for the needs of complex cognitive tasks (Rao et al., 1997; Rainer et al., 1998a). Therefore, the dorsolateral and ventrolateral subdivisions of the PFC themselves differ not so much in the nature of the information that they represent, but rather in terms of processes such as learning and maintaining different types of associations and rules. Correspondingly the dorsolateral PFC may have the ability to represent a wider range of information than the PPC.

A third category of potential functional differences has to do with further processing of information transmitted to PFC from the PPC, based on task demands, rules, or context. The ability of prefrontal neurons to resist the interference of distractors during working-memory is one such property (Constantinidis and Procyk, 2004). In the following sections, we review the properties of dorsolateral PFC and PPC in a series of cognitive functions that are unique or distinct between the two areas, and consider their functional implications. We should make clear that the review of studies in the following sections labeled "attention" and "working-memory" is somewhat arbitrary; behavioral tasks routinely require interplay of these factors and there is still debate about the fractionation of neuronal activity to these processes (Lebedev et al., 2004; Cisek and Kalaska, 2010; Gottlieb and Balan, 2010). We finally discuss the anatomical and cellular substrates that may mediate these differences.

ATTENTION

Attention is an essential cognitive process for selecting certain information in the environment to be processed in more detail, while filtering stimuli of less importance for the contingencies of the moment (Carrasco, 2011). Two distinct attentional systems have been identified: bottom-up attention, an externally evoked process in which information of a stimulus appearing in the environment is processed relatively automatically; and top-down attention, an internally evoked process in which stimuli are searched according to voluntarily selected features or locations (Itti and Koch, 2001; Corbetta and Shulman, 2002; Connor et al., 2004). Early human psychophysical studies revealed that stimuli that stand out by virtue of their relative saliency against their background attract attention and are able to be identified in parallel, without requiring search of every element in a display (Treisman and Gelade, 1980; Duncan and Humphreys, 1989). In contrast, stimuli that are not uniquely salient require volitional guidance of attention and serial inspection of elements in the display before they can be identified as targets of search (Wolfe and Horowitz, 2004). Both bottom-up and top-down factors interact for the guidance of attention in everyday experience (Wolfe, 2010). Models created to account for these psychophysical findings led to the proposal that visual features are processed into separate "feature maps" based on bottom-up activation that relies on the physical uniqueness of the stimulus in the field, and top-down activation that depends on the relevance of the stimulus to the task during visual search (Wolfe, 1994). The feature maps are then integrated into one "saliency map" (or "priority map" to denote the combined effect of bottom-up and top-down influences), according to which attention can be directed to the locus with highest activation in the map (Koch and Ullman, 1985). The existence of neural correlates of these saliency maps was only speculated at the time the concept was proposed, but distinct brain activation in response to salient stimuli has since been identified (Constantinidis, 2006). If anything, saliency maps now appear to be simultaneously present in multiple brain areas, including the PPC (Gottlieb et al., 1998; Constantinidis and Steinmetz, 2001), the PFC (Schall and Hanes, 1993; Thompson et al., 1996), and subcortical structures such as the superior colliculus (McPeek and Keller, 2002) and substantia nigra (Basso and Wurtz, 2002). In the following paragraphs, we discuss the relative roles of dorsolateral PFC and PPC in bottom-up and top-down attention.

During search, neurons in the dorsolateral PFC preferentially represent salient stimuli while responses to distractors in the presence of salient stimuli are greatly suppressed (**Figure 2**). In particular, a series of studies in the FEF have revealed that neurons represent salient stimuli that stand out in terms of color or shape (Schall and Hanes, 1993; Schall et al., 1995; Thompson et al., 1996; Sato et al., 2003). The results indicate that the PFC maintains a map of visual saliency (Schall and Thompson, 1999). Indeed, microstimulation of the FEF, below the threshold of saccade generation can improve performance in attention tasks and increase the activity of single neurons in extrastriate visual areas (Moore and Fallah, 2001; Moore and Armstrong, 2003).

Neurons in areas 7a and LIP of the PPC exhibit similar patterns of responses as dorsolateral prefrontal neurons (Constantinidis and Steinmetz, 2001; Ipata et al., 2006; Thomas and Pare, 2007; Premereur et al., 2011). These preferential responses include activity driven purely by visual saliency and are present even in subjects not trained to perform a search task (Constantinidis and Steinmetz, 2005; Arcizet et al., 2011). Similarly, posterior parietal neurons represent preferentially visual stimuli rendered salient by being presented after background stimuli had already been visible (Gottlieb et al., 1998; Kusunoki et al., 2000). Therefore, activity across the PPC can also represent the location of salient stimuli and serve as a saliency or priority map (Bisley and Goldberg, 2010). Microstimulation of LIP can also bias selection of visual targets (Mirpour et al., 2010).

Functional differences between the two brain regions have been suggested in terms of the time course of selective representation of the salient stimulus (**Figure 2**). By some accounts, the PPC represents salient stimuli with shorter latencies, suggesting that this area provides the primary representation of visual saliency,

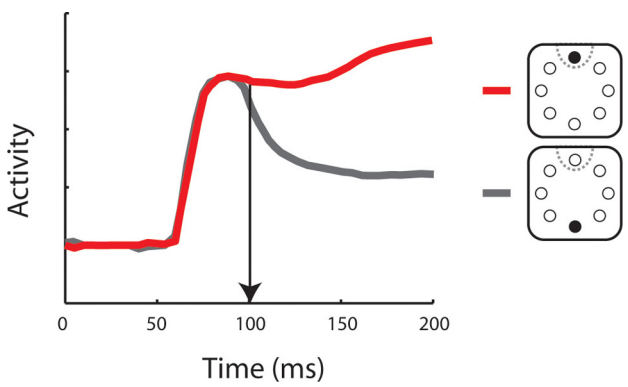

FIGURE 2 | Neuronal activity representing a salient stimulus. Schematic illustration of a post-stimulus time histogram representing neuronal responses to two stimulus conditions. Insets depict the salient stimulus appearance in (red) or out (gray) of the neuron's receptive field (dotted line). Vertical arrow indicates the time of neuronal target discrimination. The diagram was constructed based on the results of Thompson and colleagues [Thompson et al. (1997)].

which is then transmitted to the dorsolateral PFC in a serial manner (Buschman and Miller, 2007). This finding remains controversial (Schall et al., 2007) as other studies have uncovered comparable time courses of activation in the FEF and PPC, employing essentially identical stimuli and analysis methods (Thompson et al., 1996; Thomas and Pare, 2007). It is also notable that the task used in the Buschman and Miller study did not rely entirely on a bottom-up process: a cue was presented to subjects in advance to the target presentation which could also involve top-down process. In any case, prefrontal activation appears to be essential for the completion of bottom-up tasks. Muscimol inactivation of the dorsolateral PFC has been reported to lead to deficits in visual search of a pop-out stimulus (Iba and Sawaguchi, 2003; Wardak et al., 2006). In summary, it is clear that both the PPC and dorsolateral PFC represent bottom-up visual saliency, although their relative role in the guidance of bottom-up attention remains a matter of debate.

In terms of top-down attention, neurons in the PPC show dramatic modulation to stimuli that a subject selects or is cued to attend to, compared to unattended stimuli (Robinson et al., 1978; Yin and Mountcastle, 1978; Bushnell et al., 1981; Toth and Assad, 2002; Bisley and Goldberg, 2003). Interestingly, parietal responses generally decrease when stimuli appear at locations that are already attended, leading to the hypothesis that the PPC plays a crucial role in the re-orienting of attention to a new stimulus of interest (Steinmetz et al., 1994; Steinmetz and Constantinidis, 1995). A causal role of the PPC in orienting attention has been revealed by chemical inactivation experiments; both eye movements and covert attention is impaired under muscimol injections (Wardak et al., 2002, 2004; Liu et al., 2010). Conversely, electrical microstimulation induces covert shifts of attention (Cutrell and Marrocco, 2002).

Responses of dorsolateral prefrontal neurons in top-down attention are similar in many respects. Prefrontal neurons preferentially represent attended over unattended stimuli (Rainer et al., 1998b; Lebedev et al., 2004). Microstimulation of the FEF has shown behavioral enhancement in tasks that require spatial attention and increase in firing rate in visual cortical areas, providing direct evidence of attentional control by the PFC (Moore and Fallah, 2001, 2004; Moore and Armstrong, 2003). On the other hand, reversible inactivation of the FEF through muscimol injection results in attentional deficits (Wardak et al., 2006).

Comparing the functional properties of the dorsolateral PFC and PPC in top-down attention reveals few differences. The PPC has been reported to represent targets of visual search defined by top-down factors later than the dorsolateral PFC (Buschman and Miller, 2007). This finding suggests that top-down signals originate in the PFC, and are only later represented in parietal activity. Comparison of inactivation effects of the FEF and area LIP also reveal distinct patterns of errors (Wardak et al., 2004, 2006). Specifically, prefrontal inactivation affects psychophysical performance in a search task both for difficult (conjunction) conditions and easy (feature detection) conditions. On the other hand, parietal inactivation selectively impairs the hardest types of search. The results suggest subtle but distinct roles of the PFC and parietal cortex in the guidance of attention.

WORKING-MEMORY

Working-memory is the ability to flexibly retain and manipulate information in mind, according to current needs (Baddeley, 2003). It is a fundamental component of higher cognitive functions including language, reasoning, planning, and decision-making (Curtis and Lee, 2010). Baddeley proposed that working-memory encompasses a series of slave systems representing different modalities of information (the phonological loop, visuo-spatial sketchpad, and episodic buffer), which in turn are controlled by a central executive (Baddeley, 2000). Working-memory is synonymous to the earlier concept of short-term memory (Atkinson and Shiffrin, 1968), though the working-memory model emphasizes that this is not simply a buffer of incoming information but it is involved in a bidirectional flow of information to and from long-term memory. In recent years, the term visual short-term memory has been used in the literature to refer specifically to information contained in simple visual displays (e.g., with multiple colored squares appearing at different locations in the screen), not involving properties that can be represented and manipulated in memory in an abstract form (Todd and Marois, 2004).

Neurophysiological recordings from non-human primates have demonstrated persistent discharges of neurons observed after the offset of sensory stimuli (**Figures 3A,B**) that subjects were required to remember and recall (Fuster and Alexander, 1971). Furthermore, this persistent activity spanning the delay period of working-memory tasks is tuned to specific stimulus properties (Funahashi et al., 1989). For these reasons, persistent activity is generally considered as the neural correlate of working-memory, providing a mechanism for maintaining in memory the properties of a remembered stimulus (Goldman-Rakic, 1995). Recurrent connections between layer 2/3 cortical neurons are considered as the main contributor to the generation and maintenance of persistent discharges (Constantinidis and Wang, 2004). Neurons originally activated by a sensory stimulus continue to excite each other through a dense network of reciprocal connection—such as the extensive network of intrinsic connections reported in area 46 of the PFC (Kritzer and Goldman-Rakic, 1995) allowing activity to reverberate even after the original stimulus is no longer present. Although persistent activity was initially demonstrated in the PFC, it has now been observed in multiple brain regions, including other areas of the association cortex and subcortical regions such as thalamic nuclei and the basal ganglia (Constantinidis and Procyk, 2004; Pasternak and Greenlee, 2005; Rawley and Constantinidis, 2009).

Short-term memory phenomena not based on persistent activity have also been recognized. One such effect has been described in the context of tasks that require comparison of two stimuli presented in sequence. Some neurons respond differentially to the same stimulus depending on whether it matched a previous stimulus or not, and this activity is, therefore, informative about the prior stimulus (Miller et al., 1991). Non-spiking, synaptic mechanisms are thought to mediate this process (Mongillo et al., 2008; Sugase-Miyamoto et al., 2008). In the next paragraphs, we will review the properties of working-memory activity in the dorsolateral PFC and PPC and what they reveal about their common and unique roles in the maintenance of working-memory.

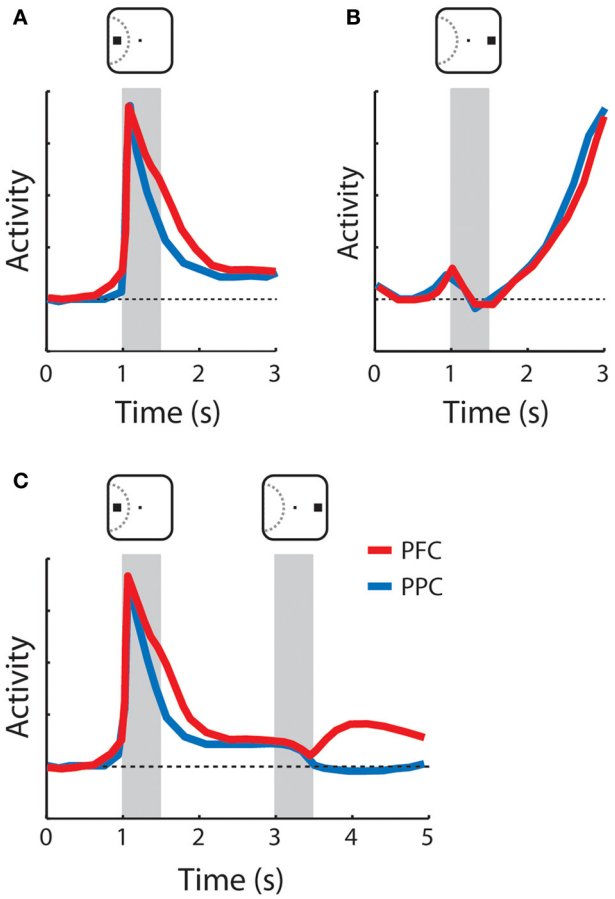

FIGURE 3 | Schematic illustration of neuronal responses with persistent activity in the prefrontal and posterior parietal cortex. Gray bars indicate times of stimulus presentations. Red and blue lines represent the activity of the prefrontal cortex and the posterior parietal cortex, respectively. Insets above the gray bars illustrate examples of stimulus location relative to the receptive field depicted with dotted curve. **(A)** Sustained activity following appearance of the cue in the receptive field. Both the prefrontal and posterior parietal cortex continuously sustained activity higher than the baseline (horizontal dotted line) after the cue offset. **(B)** Anticipatory activity following appearance of the cue out of the receptive field. No activity was elicited by the stimulus; activity accelerated during the delay period. **(C)** Responses to the cue in the receptive field followed by a non-match stimulus out of the receptive field. Prefrontal neurons maintained activity during the delay period after the second stimulus (distractor) was presented whereas the activity of the posterior parietal went back to baseline. The diagrams were constructed based on the results of Qi and colleagues [Qi et al. (2010)].

Neurons in the dorsolateral PFC, including the FEF, readily exhibit persistent activity in a wide range of tasks that require working-memory, and this activity represents attributes of the remembered stimulus such as its spatial location, shape, color, and luminance (Fuster et al., 1985; Funahashi et al., 1989; Constantinidis et al., 2001; Armstrong et al., 2009; Meyer et al., 2011). The activity of these neurons is quite heterogeneous in terms of the envelope of neuronal responses but can be classified into two broad categories: activity that appears to extend a response to the stimulus itself and is sustained into the delay period, schematized in **Figure 3A**, and activity that only begins after the offset of the stimulus and accelerates during the delay period, as shown in **Figure 3B** (Quintana and Fuster, 1992; Qi et al., 2010). We refer to these types as sustained and anticipatory, respectively. Anticipatory activity has also been associated with prospective memory of an upcoming stimulus or event (Rainer and Miller, 2002). In recent years it has become evident that performance of a working-memory task is not necessary for the emergence of working-memory activity; persistent responses are present even in naïve animals, only required to fixate after the appearance of visual stimuli (Meyer et al., 2007, 2011). Dorsolateral prefrontal neurons also exhibit activity reflective of the properties of a previous stimulus, independent of persistent discharges. A population of prefrontal neurons responds differentially to a stimulus if it appears as a match or a non-match, in delayed match-to-sample tasks (Miller et al., 1996; Pasternak and Zaksas, 2003; Kusunoki et al., 2009; Qi et al., 2012).

Posterior parietal neurons are also active in the delay period of working-memory tasks (Gnadt and Andersen, 1988; Constantinidis and Steinmetz, 1996; Chafee et al., 2005), and responses of individual neurons are tuned for the spatial location of the remembered stimulus (**Figure 3A**). Working-memory capacity represented in the activity of the PFC and PPC appears to be similar (Buschman et al., 2011). Like the PFC (**Figures 3A,B**), posterior parietal neuronal activity can be classified into sustained and anticipatory (Quintana and Fuster, 1992; Qi et al., 2010). In the PPC too, working-memory activity is present even in naïve animals, only trained to fixate (Constantinidis and Steinmetz, 2005), although this report involved only a very brief delay period. Finally, posterior parietal neurons also exhibit modulation by the match or non-match status of a remembered stimulus (Steinmetz et al., 1994; Rawley and Constantinidis, 2010).

From this review of properties, it is evident that PFC and PPC manifest very similar types of activity-related to working-memory and it is no surprise that studies comparing the activity of dorsolateral prefrontal and posterior parietal neurons in the same animals have revealed a great deal of similarities. These include similar percentages of neurons activated in the two areas, similar response magnitudes, similar temporal envelopes of responses, and similar tuning characteristics to spatial stimuli (Chafee and Goldman-Rakic, 1998; Qi et al., 2010).

Although there are common features of persistent activity in the PFC and the PPC, different properties between areas have also been identified. One difference has to do with the response patterns during maintenance of a stimulus in memory, when multiple stimuli are presented sequentially (**Figure 3C**). Prefrontal neurons represent the location of the original stimulus, actively held in memory even after the appearance of distractors (di Pellegrino and Wise, 1993; Qi et al., 2010), while posterior parietal neurons represent the most recent stimulus presentation (Constantinidis and Steinmetz, 1996). We should note, however, that the difference between the areas may be quantitative rather than qualitative. Posterior parietal neurons continue to exhibit small but significant levels of sustained activity following the presentation of a stimulus that serves to summon attention even after the appearance of a distractor (Bisley

and Goldberg, 2003), and a difference between areas was not apparent in some tasks tested in the same animals (Qi et al., 2010). A second line of evidence for functional specialization between the two regions in working-memory comes from cooling experiments. Cooling of the PFC produces more pronounced performance decreases in spatial working-memory tasks compared to cooling of the PPC, at least in terms of saccadic error around the remembered target (Chafee and Goldman-Rakic, 2000). Finally, a third proposed type of differentiation has to do with the nature of information represented in working-memory for each of the two areas. By virtue of their proximity, the ventrolateral and dorsolateral PFC was proposed to integrate information from both the dorsal and visual streams, particularly as a result of task demands (Rao et al., 1997; Rainer et al., 1998a). Later experiments indicated that parietal neurons have equivalent selectivity for non-spatial information as that described in the PFC (Sereno and Maunsell, 1998; Toth and Assad, 2002). At the same time, experiments recording activity before and after training in tasks that require integration of spatial and non-spatial information reveal that dorsolateral PFC has a clear bias toward the representation of spatial information, both before and after training (Meyer et al., 2011). Therefore, it is questionable whether information content is a significant distinguishing feature between the dorsolateral PFC and PPC in working-memory.

DISTRIBUTED PROCESSING

The previous sections have highlighted the functional dissociation between PPC and dorsolateral PFC, however, it is important to emphasize that routine execution of a range of cognitive functions depends on both areas, whether they involve distinct or identical patterns. In this sense, concurrent parietal and prefrontal activation during the execution of a cognitive task should not be viewed as a sign of redundancy but could be more appropriately interpreted as a vital element of distributed processing. The necessity of activation of both areas is revealed by the studies such as those relying on cooling to reversibly inactivate either brain area (Quintana et al., 1989; Chafee and Goldman-Rakic, 2000). Even in tasks that fail to differentiate the patterns of activity between areas such as the delayed response task, reversible inactivation of either brain area produces performance impairments, and despite continued presence of activity in the area that was not being inactivated. Behavioral events, therefore, are likely to rely on the concerted action of neurons in multiple cortical areas (Chafee and Goldman-Rakic, 2000).

NEURAL SUBSTRATES OF SPECIALIZATION

Despite the overall similarity in anatomical inputs and the parallel nature of anatomical projections between the dorsolateral PFC and PPC, a number of anatomical properties differ between these areas, including the influence of various neurotransmitter systems, the intrinsic connectivity within each area, as well as the respective connectivity with other brain regions. Computational models exploring these differences have offered significant insights into the underlying mechanisms mediating functional specialization of each area. In the following sections we will focus on the role of two neurotransmitter systems, dopamine and glutamate, and the patterns of intrinsic connectivity between excitatory and inhibitory neurons in the two regions.

DOPAMINERGIC INNERVATION

Dopamine has long been viewed as a critical factor of prefrontal function and a unique influence to the PFC compared to its cortical afferents. Dopamine preferentially innervates the frontal lobe, whereas dopaminergic innervation is largely absent from the parietal cortex (Levitt et al., 1984; Haber and Fudge, 1997). Dopamine dysregulation in the PFC has also been implicated in schizophrenia, which is linked to marked impairments in working-memory and executive function (Okubo et al., 1997; Abi-Dargham et al., 2002; Karlsson et al., 2002). Decreased prefrontal activation has been reported in animal models of schizophrenia, which alters dopamine uptake in other brain areas as well (Bertolino et al., 1999; Meyer-Lindenberg et al., 2002). Computational studies have demonstrated persistent discharges with an improved signal-to-noise ratio in networks that incorporate dopamine inputs, compared to equivalent networks without dopamine (Durstewitz et al., 2000). Dopamine innervation has also been proposed as a gating mechanism in reinforcement learning, signaling which stimuli predict reward and which are irrelevant (Montague et al., 2004).

Two families of dopamine receptors have been identified, with unique cognitive contributions. D1 dopamine receptors are widely spread in the PFC whereas D2 receptors are more abundant in the striatum (Meador-Woodruff et al., 1996). The former are generally considered responsible for prefrontal-dependent cognitive functions, whereas the latter are the main site of action of antipsychotic drugs (Remington et al., 2011). Local injections of D1 antagonists in the dorsolateral prefrontal cause impairments in performance of both working-memory (Sawaguchi and Goldman-Rakic, 1991, 1994) and attention tasks (Noudoost and Moore, 2011). D1 agonists reverse the cognitive impairments often caused by antipsychotic medication (Castner et al., 2000). D1 receptor stimulation in the dorsolateral PFC is critical for regulating the recurrent microcircuitry of the PFC (Gonzalez-Islas and Hablitz, 2003; Goldman-Rakic et al., 2004; Arnsten, 2011). Not only does D1 receptor activation facilitate excitatory persistent activity following the appearance of the preferred stimulus of a neuron (Williams and Goldman-Rakic, 1995; Seamans et al., 2001) but it also attenuates excitation to non-preferred locations and, therefore, sharpens spatial tuning during working-memory (Gao et al., 2001; Paspalas and Goldman-Rakic, 2005; Vijayraghavan et al., 2007). The relative activation of the D1 and D2 receptor systems has been implicated in the regulation of cortical dynamics, with dominance of the D1 system facilitating robust maintenance of information online, and D2 promoting flexibility between tasks and representational states (Durstewitz and Seamans, 2008).

This dynamic modulation by a variety of factors through the actions of dopamine receptors is essentially absent in the PPC and should be viewed as a unique prefrontal specialization. It should be noted, however, that the effects of dopamine modulation are complex, and experimental studies reveal non-monotonic dosage relationships (Williams and Goldman-Rakic, 1995; Zheng et al., 1999). Differential physiological effects have

also been observed depending on cortical layer, neuron type, and cellular compartment targeted (Zhou and Hablitz, 1999; Seamans et al., 2001; Gao et al., 2003; Gonzalez-Islas and Hablitz, 2003). Furthermore, the highest concentration of dopamine projections targets the medial PFC, with only a minor proportion innervating the dorsolateral PFC (Lewis et al., 1988). For this reason it is not easy to map specific functional differences between the dorsolateral PFC and PPC to particular aspects of dopamine action.

GLUTAMATE RECEPTORS

In addition to dopamine involvement, recent studies have revealed that the relative activation of glutamate receptors is important for persistent activity during working-memory (Durstewitz et al., 2000; Seamans et al., 2001; Wang, 2001; Chen et al., 2004; Wang et al., 2008; Arnsten et al., 2010). The density of NMDA receptors compared to AMPA receptors has been identified as critical in this respect (Yang and Seamans, 1996; Durstewitz et al., 2000; Seamans et al., 2001; Wang, 2001; Chen et al., 2004; Wang et al., 2008). NMDA receptors are kinetically slow and once opened leave the postsynaptic neuron in a depolarized state for a longer time, allowing subsequent postsynaptic potentials to continue generating action potentials (Wang, 1999). Resistance to interference may specifically be enhanced through an increased concentration of NMDA receptors, allowing persistent activity to survive the effect of temporary activation of a competing population of neurons (Compte et al., 2000), and a critical difference between PPC and PFC may lie in their AMPA/NMDA ratio (Izquierdo et al., 1998). Additionally the actions of dopamine itself in the PFC are partially attributed to its effects on NMDA receptors (Cepeda et al., 1992; Yang and Seamans, 1996; Seamans et al., 2001; Chen et al., 2004). Therefore, dysfunction of the prefrontal NMDA-mediated microcircuit may result in the dysregulation of dopamine system in the PFC and striatum which would cause cognitive deficits observed in psychiatric disorders (Arnsten, 2011). It has also been reported that dopamine D1 receptors modulate NMDA receptor functions in prefrontal neurons indicating that there is a reciprocal interaction between the NMDA and D1 effects (Chen et al., 2004; Gao and Wolf, 2008). Finally, reduction of NMDA activity in pyramidal circuits causes decrease in GABA, which leads to less tuned neuronal networks (Rao et al., 2000; Kinney et al., 2006).

INTRINSIC EXCITATORY CONNECTIONS

In both PPC and dorsolateral PFC, retrograde injections of anatomical tracers reveal clusters of neurons activated over a range of distances of several millimeters (Levitt et al., 1993; Kritzer and Goldman-Rakic, 1995). The elemental cortical microcircuit involves clusters of neurons with similar tuning that are interconnected through excitatory connections, and which inhibit neurons with different stimulus preferences (Goldman-Rakic, 1995). By some accounts, prefrontal pyramidal neurons exhibit the most extensive dendritic trees and highest number of spines of any cortical neurons (Elston, 2000, 2003). In the context of computational models, this would be equivalent to a larger "footprint" of connections of a single prefrontal neuron (Compte et al., 2000), which could result in greater stability of the prefrontal network. However, the precise functional consequences of these anatomical differences have not been explored in depth.

INTERNEURON TYPES

Differences in interneuron types have been proposed as another unique specialization of the PFC (Wang et al., 2004). Most cortical interneurons are parvalbumin-containing neurons, which correspond to the Fast Spiking category (Krimer et al., 2005; Zaitsev et al., 2005). In the PFC, calbindin-containing interneurons are more numerous than in other cortical areas (Elston and Gonzalez-Albo, 2003). Calbindin interneurons tonically inhibit the dendrites of pyramidal neurons in close vicinity, forming patterns of axonal connections spatially restricted across the length of a cortical column (Conde et al., 1994; Gabbott and Bacon, 1996; Krimer et al., 2005; Zaitsev et al., 2005). It has, therefore, been proposed that calbindin interneurons release pyramidal neurons from inhibition only when the pyramidal neurons have already been activated during working-memory, insulating the network from noise and distractor interference. Indeed, recent physiological evidence suggests that neurons with functional properties that fit the profile of inverted tuning neurons are more abundant in the prefrontal than the parietal cortex (Zhou et al., 2012). Calbindin interneurons may also play other unique roles in the PFC that are absent in the parietal cortex. For example, anterior cingulate projections preferentially innervate calbindin interneurons, providing a means of controlling prefrontal excitability (Medalla and Barbas, 2009, 2010).

SUMMARY AND FUTURE DIRECTIONS

The studies reviewed in this article point out that the dorsolateral PFC and PPC share a number of functional properties and are co-activated in a range of cognitive operations requiring attention and working-memory, with very similar activity patterns and time courses of activation. This evidence suggests that distributed processing recruiting the two areas is essential for the execution of cognitive functions. Progress has also been made in identifying unique functions of each area. Inactivation of the PFC causes more severe impairments in a wider range of attention, working-memory and motor functions. Additionally, the PFC is able to resist interference by distracting stimuli during working-memory.

Unresolved issues to be addressed by future neurophysiological studies include the full gamut of cognitive functions that differentiate the two areas, including the extend to which parietal and prefrontal areas exert direct influence on neuronal activity on extrastriate areas, the capacity and duration of memory traces in the prefrontal and parietal cortex and the influence of flexible rules and learning on prefrontal and parietal activity. Additionally, future experiments may reveal the nature of underlying differences that produce this functional specialization in terms of neurotransmitter systems, intrinsic connections, and connections with other brain areas.

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Differential effects of parietal and frontal inactivations on reaction times distributions in a visual search task

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The posterior parietal cortex participates to numerous cognitive functions, from perceptual to attentional and decisional processes. However, the same functions have also been attributed to the frontal cortex. We previously conducted a series of reversible inactivations of the lateral intraparietal area (LIP) and of the frontal eye field (FEF) in the monkey which showed impairments in covert visual search performance, characterized mainly by an increase in the mean reaction time (RT) necessary to detect a contralesional target. Only subtle differences were observed between the inactivation effects in both areas. In particular, the magnitude of the deficit was dependant of search task difficulty for LIP, but not for FEF. In the present study, we re-examine these data in order to try to dissociate the specific involvement of these two regions, by considering the entire RT distribution instead of mean RT. We use the LATER model to help us interpret the effects of the inactivations with regard to information accumulation rate and decision processes. We show that: (1) different search strategies can be used by monkeys to perform visual search, either by processing the visual scene in parallel, or by combining parallel and serial processes; (2) LIP and FEF inactivations have very different effects on the RT distributions in the two monkeys. Although our results are not conclusive with regards to the exact functional mechanisms affected by the inactivations, the effects we observe on RT distributions could be accounted by an involvement of LIP in saliency representation or decision-making, and an involvement of FEF in attentional shifts and perception. Finally, we observe that the use of the LATER model is limited in the context of a visual search as it cannot fit all the behavioral strategies encountered. We propose that the diversity in search strategies observed in our monkeys also exists in individual human subjects and should be considered in future experiments.

Keywords: LIP, FEF, visual search, inactivation, manual reaction times, LATER model, distribution

INTRODUCTION

The parietal and frontal cortices have both been functionally involved in saccadic eye movements, visual attention and working memory. In humans, fMRI studies have revealed co-activations of these two regions in protocols involving any of these mechanisms (e.g., Corbetta et al., 1998; LaBar et al., 1999; Hopfinger et al., 2000; Cornette et al., 2001; Astafiev et al., 2003; Koyama et al., 2004; Naghavi and Nyberg, 2005; Olivers, 2008). This co-activation is so systematic that the "parieto-frontal" network is often viewed as a functional entity in itself, that does not require that the relative complementary roles of its components be distinguished. In monkeys, this parieto-frontal network is mainly constituted of the lateral intraparietal area (LIP) and the frontal eye fields (FEF). Accordingly, both areas have neuronal activities related to visual stimulation, saccadic eye movements, visual attention and memory (e.g., Bruce and Goldberg, 1985; Gnadt and Andersen, 1988; Barash et al., 1991; Colby et al., 1996; Kodaka et al., 1997; Gottlieb et al., 1998; Hanes et al., 1998; Bisley and Goldberg, 2003; Thompson et al., 2005; Sereno and Amador, 2006).

In order to distinguish the functional roles of LIP and FEF, we conducted a series of inactivation experiments (Wardak et al., 2002, 2004, 2006) while the monkeys were performing visual saccades and covert visual search, as a measure of visual attention. We observed very different effects of the inactivation of each area on the saccadic behavior. Indeed, FEF inactivations led to large deficits up to an incapacity for the monkey to produce contraversive saccades (Wardak et al., 2006), whereas LIP inactivations led to minor or no deficits (Li et al., 1999; Li and Andersen, 2001; Wardak et al., 2002). In contrast, in the covert visual search task, the inactivation of both areas induced a comparable increase in the mean reaction time (RT) necessary to detect a contralesional target, without any change in the slope of the RT as a function of the number of items present in the visual scene (Wardak et al., 2004, 2006). Only subtle differences could be observed between the inactivation of both areas. For example, the amplitude of the RT deficit was larger for difficult visual search conditions (difficult feature search and conjunction search) than for an easy condition ("pop-out" search) following the inactivation of LIP, while the amplitude of the deficit was constant across these conditions following that of the FEF (Wardak et al., 2011). There was also no change in the mean RT necessary to detect an ipsilateral target, except after FEF inactivation in one monkey.

Although mean RT is the most widely used measure of behavioral performance, it has some limitations and may not capture all the information contained in RT data. RTs, whether manual or saccadic, do not follow a Gaussian distribution. They are better described by an ex-gaussian distribution (Ratcliff, 1979). As a result, a change in the mean RT may reflect changes in different parameters of the actual distribution: a shift of the entire distribution or an increase of the tail for example. RT distributions could also be modified without any effect on the overall mean. The aim of the present paper is thus to reanalyse the effects of LIP and FEF inactivations on the manual RTs in a covert visual search (Wardak et al., 2004, 2006) by considering the entire RTs distribution rather than just the mean RT.

From a functional point of view, a RT reflects a set of processes, ranging from the visual processing to decision mechanisms. The effect of LIP and FEF inactivations on any of these processes will thus affect the RTs and their distribution. The LATER model, developed by Carpenter (Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Reddi et al., 2003), provides an interesting framework for RT analysis. Indeed, it postulates that RTs are determined by the time taken by a decision signal to rise linearly, in response to the presentation of visual information, up to a threshold at which a response is initiated. This model considers the whole RT distribution and proposes that it can be modified either by a change in the rate of information accumulation (i.e., visual, perceptual processes) or by a change in the decision threshold (i.e., decision, cognitive, top-down processes). Both LIP and FEF have been proposed to accumulate evidence in favor of saccadic motor plans (e.g., Hanes and Schall, 1996; Shadlen and Newsome, 1996). However, these areas also contain visual and visuomotor neurons that have been shown to represent the visual saliency (Gottlieb et al., 1998; Thompson and Bichot, 2005) and to accumulate perceptual information (Shadlen and Newsome, 1996; Ding and Gold, 2012), that could lead to a perceptual decision about the presence of a target in the visual scene, even in a non-saccadic context (Ibos, Duhamel and Ben Hamed, submitted). In this study, we thus consider the possible involvement of LIP and FEF in a perceptual decision, and not in a motor decision like in saccadic tasks. According to several papers, the computation of this perceptual threshold or criterion could be internal to the areas accumulating the perceptual evidence (Wang, 2002; Machens et al., 2005; Wong and Wang, 2006). As the LATER model can also be effective in manual contexts (Madelain et al., 2007), it could provide a statistical evaluation of whether the accumulation process or the decisional threshold is altered by the focal inactivations of either area.

MATERIALS AND METHODS

SUBJECTS AND EXPERIMENTAL SETUP

Two monkeys (Monkey M, *Macaca mulatta*, and Monkey G, *Macaca fascicularis*) weighting around 6 kg participated in these experiments. We followed procedures in compliance with the guidelines of European Community on animal care (European Community Council, Directive No. 86-609, November 24, 1986). All the protocols used in this experiment were approved by the animal care committee (Department of Veterinary Services, Health and Protection of Animals, permit number 69 029 0401) and the Biology Department of the University Claude Bernard Lyon 1. Each monkey underwent two surgical sessions under propofol or isoflurane anesthesia to prepare for chronic recording of eye movements and extracellular cortical recordings. During the first surgery, the animals were implanted with scleral search coils (Judge et al., 1980) and a head-restraining device. A craniotomy was made over the left intraparietal sulcus, and a stainless-steel recording chamber was implanted to allow access to LIP with microelectrodes and injection needles. During the second surgery, a craniotomy was made over the left arcuate sulcus to access FEF in both monkeys.

Throughout the duration of the experiments, the monkeys were seated in a primate chair with their head restrained, facing a tangent translucent screen 35 cm away, which spanned ±55° of the visual field. A mechanical lever, which could be displaced only vertically, was fixed on the chair at hand level in front of the monkey. The contact between the monkey and the lever, and the press onto the lever, were electrically detected. Behavioral paradigms, visual displays, and storage of both neuronal discharge and eye and hand movements were under the control of a personal computer running a real-time data acquisition system (REX) (Hays et al., 1982). Visual stimuli were back-projected onto the screen by a Davis (Drammen, Norway) DL-450 video projector. Eye movements were recorded with the magnetic search coil technique (Primelec, Zurich, Switzerland), and horizontal and vertical eye positions were digitized at 250 Hz. All data analyses were performed off-line.

BEHAVIORAL TASK

The monkeys were trained to perform a covert visual search. This task required the monkey to maintain fixation on a central fixation point and search, while keeping their eyes on the fixation point, in the visual periphery for the presence of a predefined target in an array containing two, four, or eight items. A trial started when the monkey's hand was in contact with the lever and then the central fixation point appeared. From 300 to 1000 ms after the foveation of the fixation point, up to three visual search displays appeared in succession, each lasting 200 ms, separated by a 1000 ms blank interval. The monkeys had to press the lever within 900 ms after the appearance of a display, which contained the target. If no target was present, the monkeys refrained from responding and waited for the next display without breaking fixation. The target appeared in the first, second, or third display with equal probability, hence pressing the lever at random would result in 33.3% of correct answers. Trials were interrupted if the monkey pressed the lever when no target was present or failed to maintain fixation. Both monkeys used their right hand to answer. Within a given trial, successive displays contained the same number of items, but the number of items per display varied randomly from one trial to the next. The visual items were circularly distributed at 10° of eccentricity, half on the left side and half on the right side of the fixation point. Visual fixation was controlled within a 2.5° or 3° wide window of tolerance.

Other than the covert visual search task on which the current study focuses, both monkeys were also trained on visually- and memory-guided saccade tasks (Wardak et al., 2002, 2006) and competition/extinction saccade task (Wardak et al., 2002 for

Monkey M, not published for Monkey G). The only training difference between the two monkeys is that Monkey M was trained to an overt version of the visual search task (Wardak et al., 2002) before being trained for the covert visual search, whereas Monkey G never learned the overt task.

VISUAL STIMULI

The fixation point was a gray cross. The target was a pink diamond shape. We tested three visual search conditions (**Figure 2A**). In the conjunction search condition, the target was identified by a specific combination of two visual features, one shape and one color (always the pink diamond). The other combinations constituted the distractors (orange diamond, pink star, and orange star). All subtended the same visual angle of 1.8°. Two additional conditions were tested in which the target differed from the distractors by a single visual feature. In the easy feature search condition, there was only one distractor type of the same shape as, but different color from, the target (a blue or green diamond). In the difficult feature search condition, the distractors were heterogeneous and consisted of three different shapes of the same color as the target (pink).

LIP AND FEF IDENTIFICATION

Identification of LIP was based on single-cell recordings. Single-neuron activity was recorded extracellularly with microelectrodes (Frederick Haer, 1–2 MΩ at 1 kHz), which were lowered through stainless steel guide tubes by means of a hydraulic microdrive (Narishige). Neuronal responses were recorded in the lateral bank of the intraparietal sulcus during visually guided saccade task, memory-guided saccade task, and fixation with passive visual stimulation to determine precisely both the location and extent of LIP and its borders with other well-characterized neighboring areas. Visual, memory, and/or saccadic neuronal activity were observed and used to identify LIP (Gnadt and Andersen, 1988; Colby et al., 1996), contrasting with the motion-, tactile-, arm-, and hand-related responses of the neighboring regions VIP, MIP, and AIP (Colby et al., 1993; Sakata et al., 1995; Johnson et al., 1996). We observed the rough topographic organization of the visual field representation in LIP as described previously by Ben Hamed et al. (2001). This representation helped us to choose the injection points for muscimol experiments in order to cover the whole area LIP and to avoid diffusion of the muscimol in the neighboring areas. Injection tracks corresponded to recording sites with both visual and saccadic-related activity.

In one monkey (Monkey M), the FEF was first located by using single-cell recordings. Neuronal responses were recorded mainly in the anterior bank of the arcuate sulcus, while the monkey was performing a memory-guided saccade task. Visual and saccadic neuronal activities were recorded andused to identify FEF. The localization of the FEF was confirmed in Monkey M and determined in Monkey G by using electrical microstimulation. The stimulations were delivered by a stimulator (Neurolog) through tungsten microelectrodes (50–500 kΩ at 1 kHz; Frederick Haer). Stimulations consisted in trains of biphasic pulses (pulse duration, 0.25 ms; train duration, 70 ms; stimulation frequency, 300 Hz) of varying intensity (range tested: 5–150 Å). The FEF was defined as the cortical region, the stimulation of which elicited saccadic eye movements for an intensity $<50\,\mu$A (Tehovnik and Sommer, 1997). We observed the known topographical organization of the FEF, along the arcuate sulcus, with very small saccades elicited in the most ventrolateral part and large saccades in the most dorsomedial part of the FEF (Bruce et al., 1985). This representation helped us to choose the injection points for muscimol experiments to cover the whole area FEF and to avoid diffusion of the muscimol in the neighboring areas. Injection tracks corresponded to sites evoking saccades at very low intensity (10–40 μA).

LIP AND FEF INACTIVATION

A solution of muscimol (Sigma, St. Louis, MO) in saline (8–12 μg/μl for LIP injections, 3–8 μg/μl for FEF injections) was injected with a 5 μl Hamilton syringe connected to a 29 gauge stainless steel needle. Muscimol, a GABAA agonist, was used because it interacts specifically with GABAA receptors and does not induce conduction block in fibers of passage. For LIP inactivation, three needle tracks were performed in each experiment and, along each track, two injections were made at distinct physiologically characterized sites of LIP, separated by 2–4 mm. For FEF inactivation, three needle tracks were performed in each experiment and, along each track, one injection was made. The volume injected at each site was 0.5 μl and was delivered continuously in 7.5 min by an automatic pump system. The total amount of muscimol injected in each experiment ranged between 24 and 36 μg for LIP inactivation, and between 4.5 and 12 μg for FEF inactivation. In Monkey G, three injections were made into the left parietal cortex and seven injections in the left frontal cortex. In monkey M, five injections were made in the left parietal cortex and seven injections into the left frontal cortex.

Both monkeys used their contralesional right hand to respond. After the injections were completed, we tested for the onset of muscimol effects with an extinction task (showing as an ipsilateral bias in choice to simultaneous bilateral presentation of two flashed visual targets), which is a reliable online behavioral marker of LIP inactivation effect (Wardak et al., 2002) or with a visual saccade task which is a reliable online behavioral marker of FEF inactivation effect (Wardak et al., 2006). This effect generally started 15–60 min post-injection. The order of the different task conditions was counterbalanced across inactivation experiments, and control data were always obtained on the following day and in the same order of presentation. The entire duration of behavioral testing never lasted more than 3 h, well within the accepted range of muscimol effects (Malpeli, 1999; Martin and Ghez, 1999). Two physiological saline injections, one into LIP and one into FEF, in Monkey M served as a further control for the specificity of the effects.

DATA ANALYSIS

Preliminary data analysis did not indicate a systematic tendency for LIP or FEF inactivation to affect particular target locations within the contralesional hemifield. Thus, for the sake of presentation clarity, results for different target locations were grouped by hemifield. Intrinsic to the design of our visual search task, with its sequential presentation of up to three stimulus arrays, is the possibility that monkeys learned to anticipate the necessary presence

of the target on the third array, after two arrays with no target in them. Surprisingly, no effect of the order of presentation within a trial was observed on RT. Third array targets were not responded to faster than first or second array targets, suggesting that the three stimulus arrays were processed in the same manner [two-way ANOVA, number of items × presentation order; Monkey G, presentation order factor, $p > 0.60$ ($p > 0.40$), interaction $p > 0.08$ ($p > 0.20$) for the LIP (FEF) experiments data; Monkey M, presentation order factor, $p > 0.09$ ($p > 0.38$), interaction $p > 0.37$ ($p > 0.11$) for the LIP (FEF) experiments data]. Therefore, all subsequent statistical analyses were conducted on pooled data from the three types of trials. Behavioral data obtained during the sham injections of saline solution showed no significant difference with control sessions. To increase the statistical power of the analyses presented below, we pooled the result from all experiments, and we compared these data with pooled data obtained on the day after each inactivation experiment.

We used the LATER model to plot and interpret the changes in RT distributions (Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Reddi et al., 2003). This simple model proposes that a decision signal rises linearly, in response to information about a target, to a threshold at which a response is initiated, at a rate that varies from trial to trial with a gaussian distribution (**Figure 1A**, left panel). Cumulative RT distributions are plotted as reciprobit plots, so that each distribution corresponds to a line (**Figure 1A**, right panels). The model originally makes two alternative predictions. A change of RT distribution can be explained by a change of accumulation rate, in which case the two lines corresponding to the each RT distribution are shifted one with respect to the other but remain parallel (shift, **Figure 1B**, left). Else, a change in RT distribution can be explained by a change of the decisional threshold, in which case the two lines swivel one with respect to the other and intercept at time = infinity (swivel, **Figure 1B**, middle). Finally, some authors introduced a third possibility of change (Madelain et al., 2007), which corresponds to a modification of the variance of the accumulation rate (σ), in which case the two lines rotate one with respect to the other around the median (rotate, **Figure 1B**, right). Specifically, for estimating the likelihood that the two RT distributions that are being compared result from a change in the accumulation rate, we identify the LATER model parameters (accumulation slope, RT distribution standard deviation, noise distribution standard deviation and the factor of accumulation rate change between the two conditions) that maximize the likelihood of observing these two distributions. For estimating the likelihood that the two RT distributions that are being compared result from a change in the decision threshold, we identify the LATER model parameters (accumulation slope, RT distribution standard deviation, noise distribution standard deviation, and the factor of decision threshold change between the two conditions) that maximize the likelihood of observing these two distributions. For estimating the likelihood that the two RT distributions that are being compared result from a change in the variance of the accumulation rate, we identify the LATER model parameters (accumulation slope, RT distribution standard deviation, noise distribution standard deviation, and the factor of RT distribution standard deviation

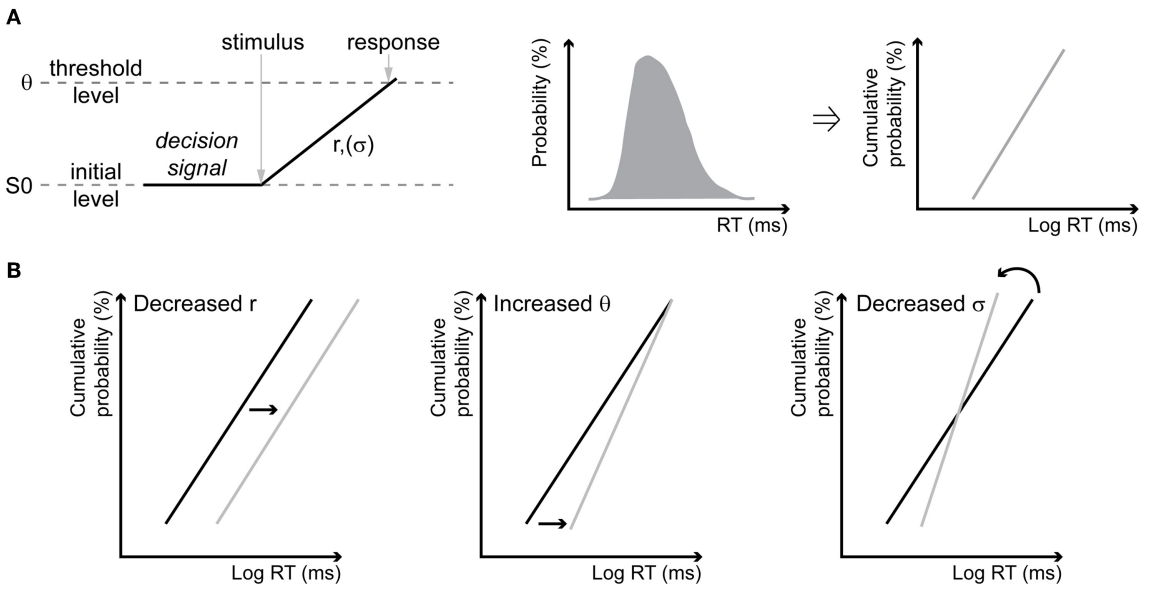

FIGURE 1 | The LATER model and its hypotheses. (A) Schematic illustrations of the LATER model. Following the presentation of a stimulus, a decision signal rises linearly, with an accumulation rate *r* that has a variance σ, from a baseline value S0 to a decision threshold θ, at which point the response is produced (left). The cumulative reaction times distribution (middle) is plotted on a probit scale with a reciprocal time axis (right) resulting in a line according to the model (called reciprobits in the text). **(B)** Predictions of the model. A change in the accumulation rate *r* results in a shift of the reciprobit (*shift*, left). A change in the threshold θ results in a swiveling of the reciprobits, intercepting at time = infinity (*swivel*, middle). In addition to the initial hypotheses, some authors (Madelain et al., 2007) have also proposed that a change in the variance σ results in a rotation of the reciprobits around the median (*rotate*, right).

change between the two conditions) that maximize the likelihood of observing these two distributions. Concurrent hypotheses were tested one against the other by evaluating which one is more likely using pair wise chi-square tests.

RESULTS

REACTION TIMES DISTRIBUTIONS IN CONTROL CONDITION

In an overt visual task, subjects' behavior is usually described in terms of number of saccades. When the task is covert, as in our case, the relevant measure is mean RT. In easy visual feature search tasks, classically called "pop-out" tasks, mean RT is constant whatever the number of items in the search array (**Figure 2B**, blue lines). In more difficult visual search tasks, mean RT increases as a function of the number of items (**Figure 2B**, difficult feature search, green lines, and conjunction search, red lines). Both monkeys thus show classical behavior.

Figure 3 shows the RT distributions plotted as reciprobits (LATER model), as a function of the search condition and number of items. The first result is that, in the easy feature search condition, the RT distributions are indistinguishable and unaffected by the number of items in the search array, for both monkeys (blue lines). For the two difficult conditions, we observe: (1) an effect of the number of items on the distributions; (2) a difference between the two monkeys. We will first consider the behavior of Monkey M (**Figure 3A**). For the two difficult conditions (difficult feature search: green; conjunction search: red), the reciprobit plots are shifted when the number of items in the visual scene increases (likelihood shift > swivel for each 2 by 2 comparison, $p < 0.05$ for the three comparisons). According to the LATER hypotheses, this result means that, when the number of objects in the visual scene increases, the rate of information accumulation decreases. This suggests that Monkey M processed the different items of the visual scene in parallel.

The results are different for Monkey G. As can be observed in **Figure 3B**, the reciprobits for the difficult feature and conjunction search conditions do not look parallel, the lines start from the same point (except one) and then diverge. None of the LATER hypotheses (**Figure 1B**) fits this profile (likelihood is still higher for shift, significant for the 2 vs. 8 items comparison, and for the 2 vs. 4 items in the conjunction condition). Historically, target detection in a visual search task has been proposed to rely on two possible mechanisms, either a parallel or a serial mechanism (e.g., Treisman and Gelade, 1980; Nakayama and Silverman, 1986; Wolfe et al., 1989). A parallel processing of the visual scene would result in a shift in the reciprobit plots, as seen for Monkey M, because the more objects are present the more have to be processed in parallel, thus decreasing the rate of information accumulation. Could a serial processing account for the reciprobit plots of Monkey G? The fact that the reciprobits originate in the same point indicates that the earliest target detections Monkey G is able to produce are not affected by the number of items in the visual scene, fitting with a serial mechanism. In order to test for this serial hypothesis, we compared the real RT distributions for the difficult feature search condition (**Figure 4**, left) to

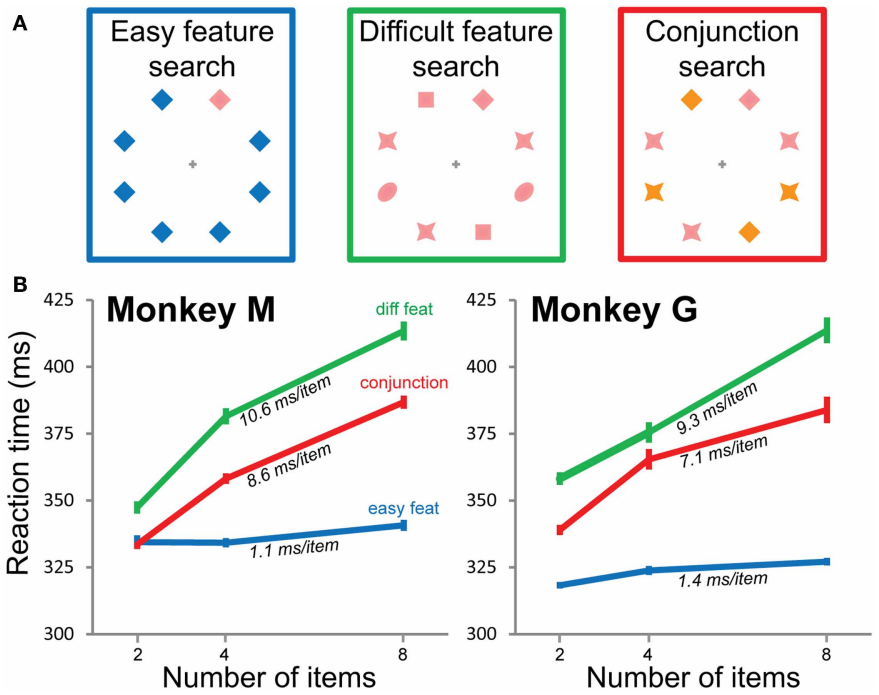

FIGURE 2 | Visual search conditions and mean reaction times. (A) Three search conditions. The target is always the pink diamond, that can be presented along blue diamonds (easy feature search, blue, left), other pink objects (difficult feature search, green, middle), or other combinations of pink/orange and diamond/star (conjunction search, red, right). **(B)** Mean reaction times in the three search conditions for both monkeys as a function of the number of items in the visual scene. The slope for each condition and monkey is indicated on the corresponding curve. The three search conditions are always coded with the same colors in all the figures: blue = easy feature search, green = difficult feature search, red = conjunction search.

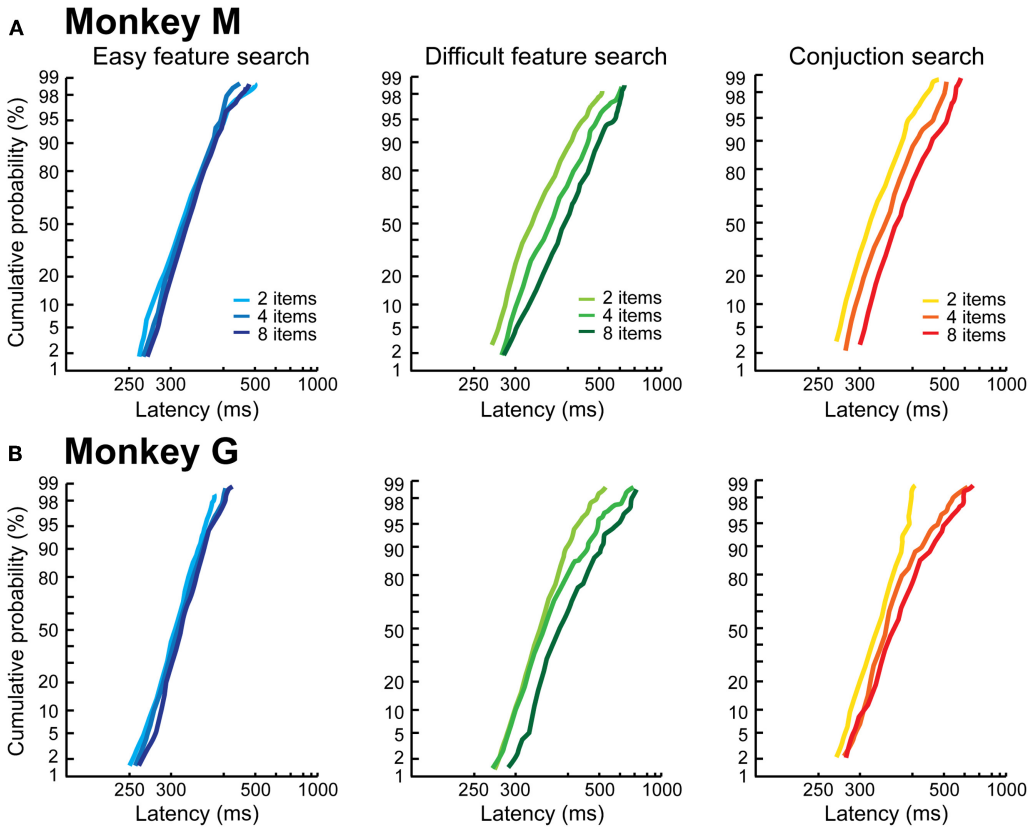

FIGURE 3 | Control reaction time distributions as a function of the search condition. The distributions are plotted as reciprobits, as a function of the number of items, in Monkey M **(A)** and Monkey G **(B)**.

simulated distributions under the hypothesis of a serial mechanism (**Figure 4**, middle). In classical visual search experiments in humans (e.g., Treisman and Gelade, 1980), the slope of the mean RT as a function of the number of items is used to estimate the timing of a single attentional shift. In our case, the slope for the difficult feature search in Monkey G is 9.3 ms/item (**Figure 2B**). For our simulation of the serial hypothesis, we thus used the easy feature search RT distribution as the basic distribution in Monkey G, for which only one attentional shift is necessary, and combined it with as many identical distributions, shifted in time by our experimental estimate of attentional spotlight shift time, as there were items still to be explored in the search array (the serial hypothesis proposes that the target is equi-probably found after 1, 2, …, n shifts of attention for a visual scene containing n items). As can be seen in **Figure 4** (middle panels), the distributions resulting from this simulation do not match the real distributions (left panels), and the reciprobit plots are more parallel than diverging. Moreover, these simulated distributions fail to replicate the late RTs of the real distributions (black arrows).

Several aspects can account for this. First, 9.3 ms is very short for an attentional shift if we consider what has been estimated in humans. In visual search, the fastest attentional shift has been estimated around 50 ms (Wolfe, 1998; Wolfe et al., 2000; Horowitz et al., 2004). Using a dual stream task, Ibos et al. (2009) have estimated that an inter-hemispheric shift lasts around 55 ms, while an intra-hemispheric shift lasts around 38 ms. Using the same inter-hemispheric task in monkeys, we estimated an attention shift to last around 30 ms (unpublished data). This more plausible estimate in attention shift time will have as effect to produce more late RTs in the simulation. Second, it has been shown that, in an overt visual search task, subjects are not systematic and that they always re-explore some of the items. Nothdurft et al. (2009) estimated that there is 7% of re-exploration, whatever the number of items in the visual scene. Re-exploration could thus explain the late RTs in the tail of the real distributions and their absence from the simulated data. Third, it has been shown that, in an overt task, saccades that are not directed to the target usually land on the distractors that are the closest in feature to the target (Bichot and Schall, 1999). The same result is also obtained in a dual covert visual search task (Zenon et al., 2008, 2009a). This suggests that visual search, instead of calling on purely serial or purely parallel processes, actually involves a combination of serial shifts with a parallel pre-analysis of the scene. This should correlate with targets being preferentially found with a small number of attentional shifts, without excluding trials in which numerous shifts are needed to find the target (more shifts than just the number of items in the search array). An example of such a semi-serial scenario is presented in **Figure 4** (right panels), favoring small numbers of shifts, with 7% of re-exploration (number of shifts > number of items), and a single shift lasting 30 ms. This

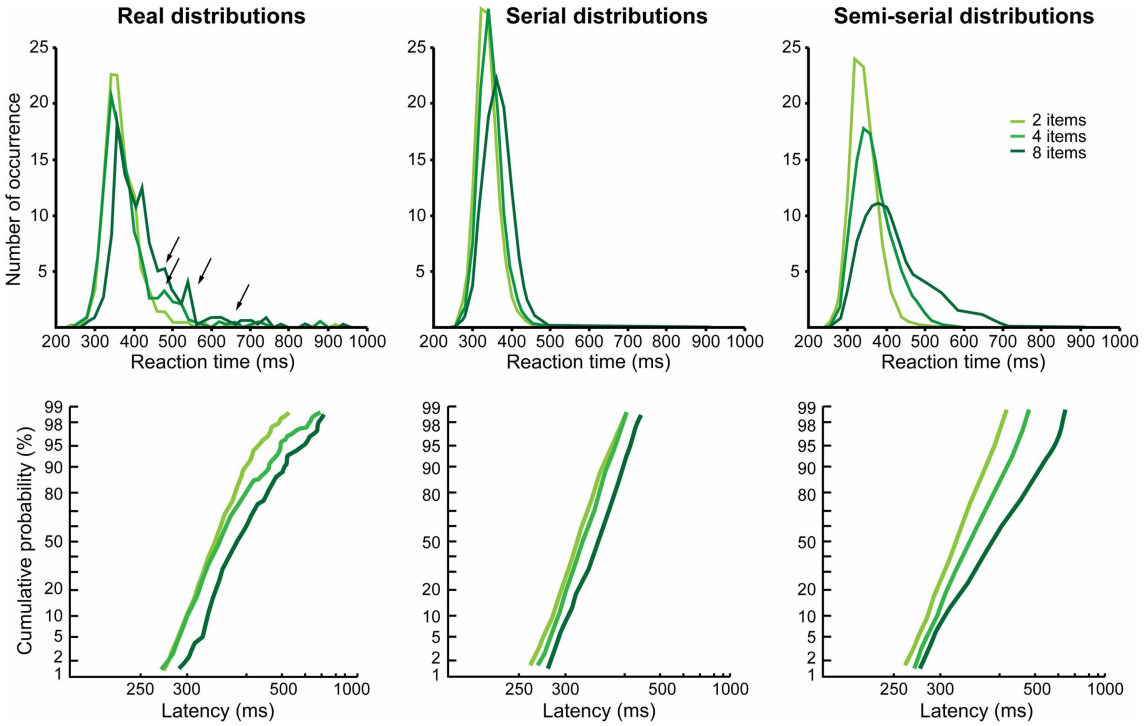

FIGURE 4 | Real and simulated reaction times distributions for the difficult feature search condition in Monkey G. On the left, the real distributions and their corresponding reciprobits are shown as a function of the number of items (same data as in **Figure 3B**, middle panel). Black arrows correspond to late reaction times bumps in the distributions that could correspond to re-exploration (see text and below). The middle distributions correspond to a simulation of a purely serial search (the easy feature search distribution of Monkey G is used as the distribution for one attentional shift and, as the number of objects increases, we add the same distribution shifted by the timing we evaluated for a single attentional shift, estimated thanks to the slope of the mean reaction time in **Figure 2B**). The right distributions correspond to a simulation of a semi-serial search, combining parallel and serial processes. We used: (1) the easy feature search distributionas the distribution for one attentional shift; (2) an evaluation of 30 ms as the timing of a single attentional shift; (3) an exploration pattern that favors small numbers of shifts to find the target, but also supernumerary shifts corresponding to 7% of re-exploration of already explored objects (2 items: 70% of 1-shift +23% of 2-shifts +7% of 3-shifts; 4 items: 35% of 1- and 2-shifts +11.5% of 3- and 4-shifts +3.5% of 5- and 6-shifts; 8 items: 17.5% of 1-, 2-, 3-, and 4-shifts +5.75% of 5-, 6-, 7- and 8-shifts +1.75% of 9-, 10-, 11-, and 12-shifts).

simulation achieves a better replication of the real distributions and their characteristics, in particular the facts that the reciprobit plots start around a same point and diverge. A perfect fit of the data would require a precise individual estimation of several parameters of the search behavior: exact timing of the shift, difference between an intra- and an inter-hemispheric shift (Ibos et al., 2009) and exact proportion of trials with a small/large number of shifts.

To conclude this section, our data show that both monkeys have different behavioral strategies, and that the LATER model is well suited to describe a parallel processing of the visual scene as observed in Monkey M. For more complex behaviors involving, as in the case of Monkey G, serial processes, this model does not seem to provide an informative description of the functional processes underlying the RT distributions.

EFFECT OF LIP INACTIVATION

LIP inactivation causes an increase in the mean RT necessary to detect a contralesional target, while no effect is observed for an ipsilesional target (Wardak et al., 2004). However, when the whole distribution is considered, a difference in the detection time of both ipsi- and contralesional targets between the control and inactivation condition is observed. Because the same effect is observed whatever the number of search items, and for sake of clarity, in the following, we pooled the data over search array configurations.

The effect of LIP inactivations on RT contralesional distributions is particularly clear in Monkey M. As can be observed in **Figure 5A**, the reciprobit inactivation plots (dashed lines) seem to swivel compared to the control data (solid line). This effect is significant in one of the search conditions, and marginally significant for another condition (easy feature $p < 0.02$, conjunction $p = 0.072$, difficult feature: likelihood swivel = likelihood shift). For Monkey G, only a tendency, going in the same direction, is observed for the difficult feature search condition (swivel $p = 0.1$), but globally there is no significant trend. Thus, at least in Monkey M, the effect of LIP inactivation appears to mainly affect the decision threshold.

Contrary to what was found when considering only the mean RT, an effect of LIP inactivations is observed on the ipsilateral distributions, especially in Monkey M. However, as can be observed in **Figure 5B**, this effect on the reciprobit plots is neither a shift

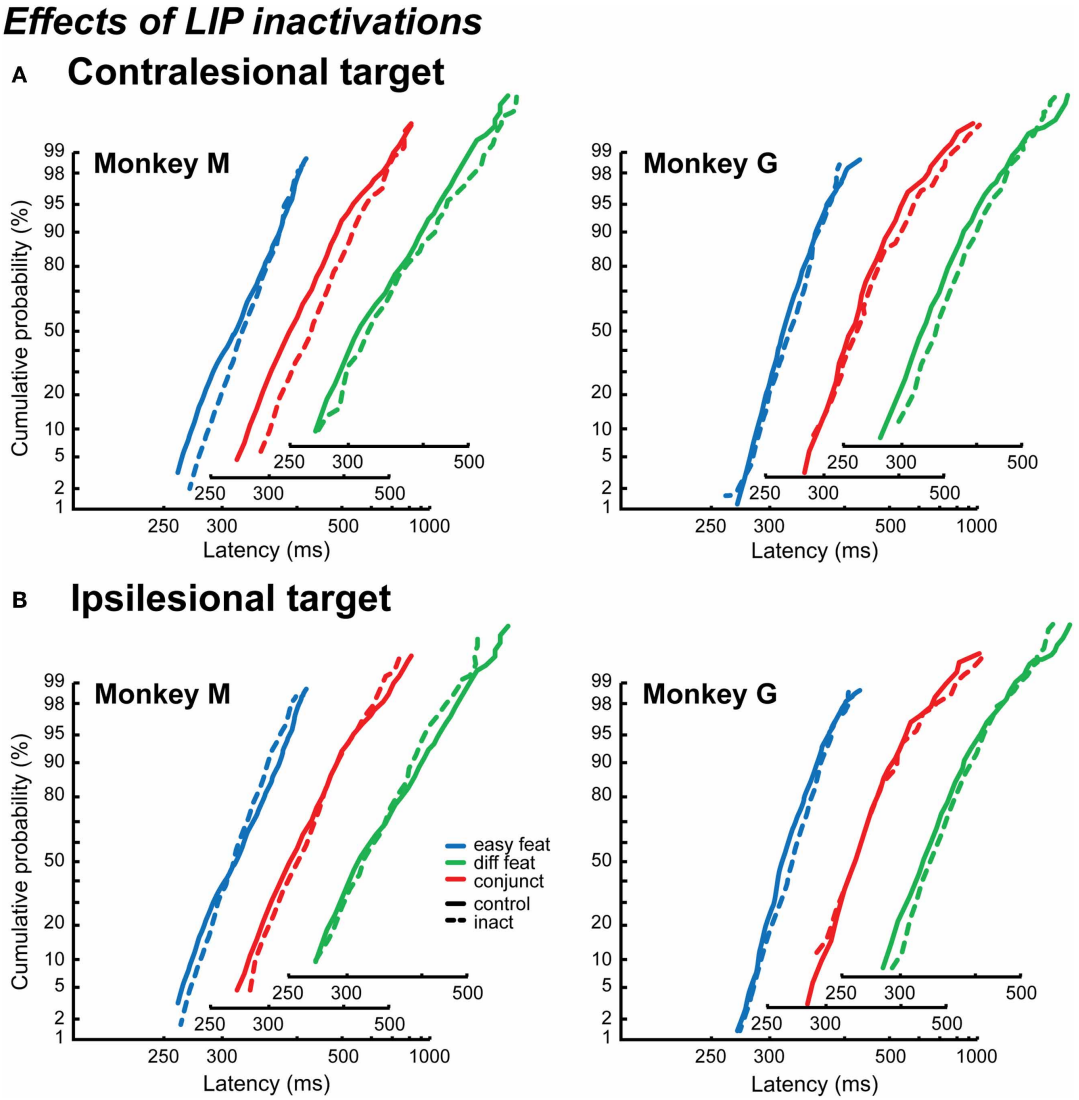

FIGURE 5 | Effects of LIP inactivations on reaction time distributions. The distributions are plotted as reciprobits for the contralesional targets **(A)** and the ipsilesional targets **(B)**, in Monkey M (left) and Monkey G (right). The different numbers of items conditions are cumulated, for the control conditions (solid lines) and the inactivation conditions (dashed lines). The x-axis is slightly shifted for the different search conditions in order to show the results more clearly.

nor a swivel, but rather a crossing of the lines. This kind of effect on the reciprobits has been observed by authors who manipulated the RT distribution of their subjects thanks to feedback, and it was specifically associated to a reduction in the variability of the distribution (Madelain et al., 2007). In the LATER model, this corresponds to a modification in the variance of the accumulation rate (σ), the result of which is a rotation of the two reciprobit lines one with respect to the other around the median (rotate, **Figure 1B**, right; Madelain et al., 2007). When including this rotation hypothesis to the LATER model, in addition to the swivel and shift hypotheses, it appears to explain Monkey M's results best (rotate vs. shift: $p < 0.05$ for easy featureand conjunction, marginally significant $p = 0.068$ for difficult feature search; rotate vs. swivel: $p < 0.05$ for easy and difficult feature search). None of these three hypotheses conclusively accounts for Monkey G ipsilesional distributions.

Focusing on Monkey M, we show that LIP inactivations affect the variance of the RT distribution for detecting an ipsilesional target. Why would it not affect also the variance of the RT distribution for a contralesional target? In fact, we cannot exclude this possibility. One limitation of the LATER model is that we cannot differentiate statistically a change of the decisional threshold (swivel) from a change in the accumulation rate taking place at the same time as a change in the variance (shift + rotate).

EFFECT OF FEF INACTIVATION

The effects of FEF inactivations on RT distributions are very different from those of LIP inactivation (**Figure 6**). As for LIP

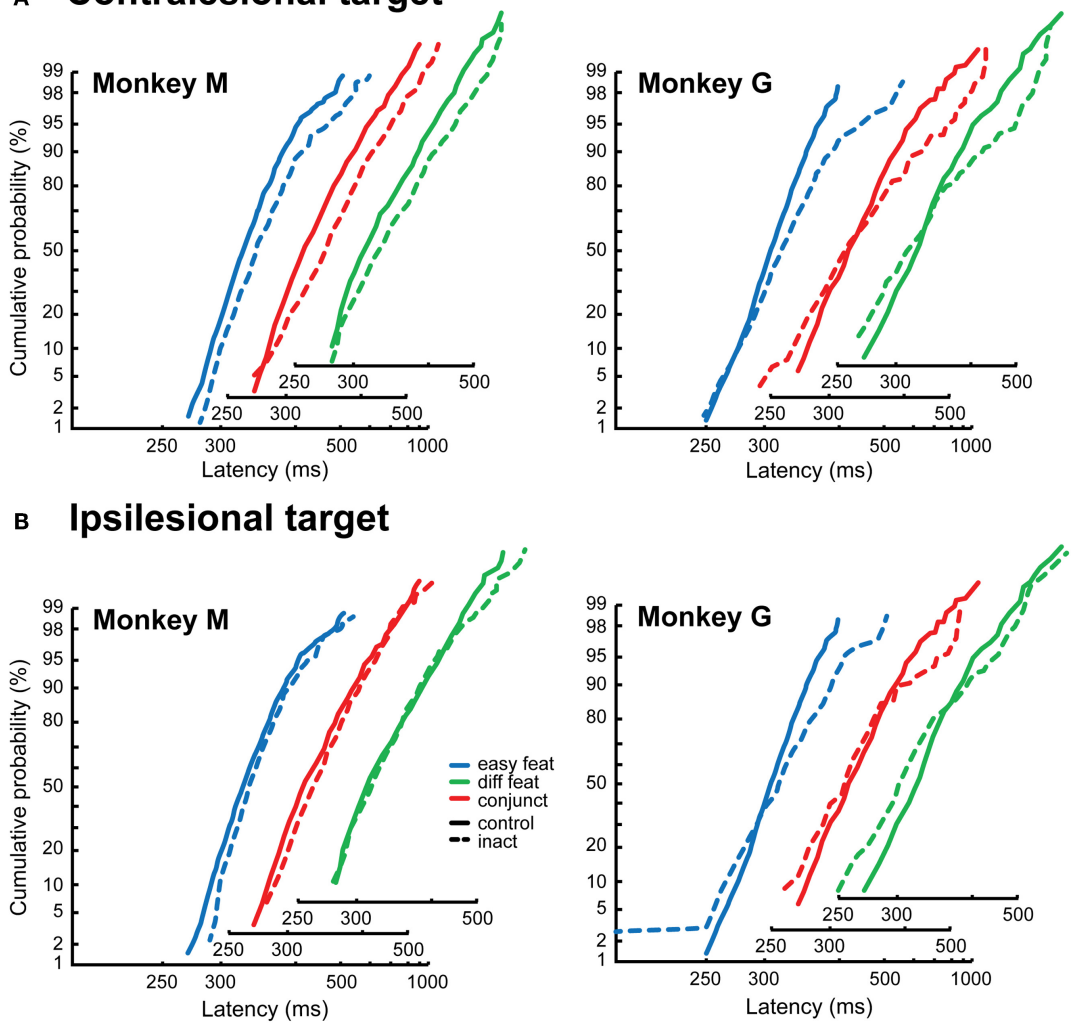

FIGURE 6 | Effects of FEF inactivations on reaction time distributions. The distributions are plotted as reciprobits for the contralesional targets **(A)** and the ipsilesional targets **(B)**, in Monkey M (left) and Monkey G (right). The different numbers of items conditions are cumulated, for the control conditions (solid lines) and the inactivation conditions (dashed lines). The x-axis is slightly shifted for the different search conditions in order to show the results more clearly.

inactivation results, we pooled the data for the different numbers of items.

As can be seen in **Figure 6**, the results from Monkey M and Monkey G are very different and are reminiscent of the different visual search strategies we describe in the control condition for each of them. In Monkey M, the reciprobit plots corresponding to the detection of a contralesional target (**Figure 6A**) are shifted with respect to the control condition for the three search conditions (likelihood shift > swivel > rotate, $p < 0.01$ for shift vs. swivel in the three conditions). This would correspond to a decrease in the accumulation rate. The effect on the ipsilesional reciprobit plots is smaller (**Figure 6B**) and no particular LATER hypothesis fits with the three search conditions (no significant difference between the shift and the swivel hypotheses). In Monkey G, we observe a rotation of the reciprobits, both for a contralesional and an ipsilesional target, in the three search conditions (**Figures 6A** and **B**; likelihood rotate > shift and swivel, $p < 0.003$ for all the comparisons), corresponding to an increase in the accumulation rate variance. The observations for ipsilesional target detections are very interesting as no significant effect was obtained when considering the mean RT independently of RT distribution (Wardak et al., 2006). A surprising result is also obtained in Monkey G for the easy feature search condition when the target is ipsilesional: we observe fast RTs, creating a second line in the reciprobit plot. **Figure 7** shows that this result appears consistently for the three different

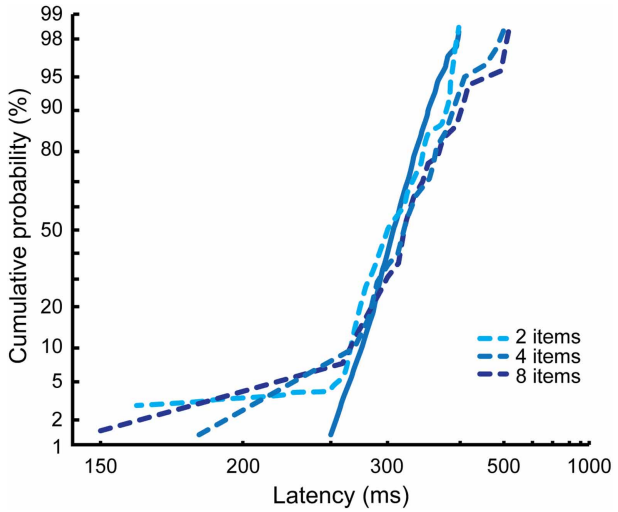

FIGURE 7 | Effects of FEF inactivations on reaction time distributions for ipsilesional targets in the easy feature search condition in Monkey G. The different numbers of items conditions are cumulated for the control condition (solid line), but represented independently for the inactivation conditions (dashed lines).

numbers of items in the easy feature search configuration: these early RTs are comprised between 150 and 250 ms and correspond to less than 10% of the total distribution.

DISCUSSION

In the present work we reanalyze the effects of LIP and FEF inactivations on the monkeys' behavior in visual search tasks (Wardak et al., 2004, 2006) by considering the entire RT distributions and not only the mean RT. We use the LATER model to help us identify the possible functional mechanisms affected by these inactivations. We find that (1) the behavioral strategy to find the target differs between the two monkeys; (2) the effects of LIP and FEF inactivations are different, suggesting that different mechanisms are affected.

In the control condition, in the easy feature search condition, adding items affects neither the mean RT (**Figure 2B**) nor the RT distributions (**Figure 3**). However, we observe a different effect of adding items in the visual scene on the RT distributions of both monkeys in the two difficult search conditions. In Monkey M, adding items results in shifting the RT reciprobit plots. According to the LATER model, this corresponds to a decrease in accumulation rate, suggesting a parallel processing strategy. Indeed, adding items adds information in the visual scene representation and thus, in the context of a purely parallel target detection strategy, is expected to increase the time needed to reach a detection decision threshold. In Monkey G, the RT distributions corresponding to the different number of items conditions do not match any of the LATER hypotheses. We propose that, the best hypothesis that fits the data (i.e., reciprobit plots that start from a single point and then diverge as observed in **Figure 3**), is that of a combination of parallel and serial processes under the following constraints: (1) the target is mostly found after a small number of attentional shifts though in some trials more shifts are necessary, (2) some items of the visual scene can be visited more than once (corresponding to the re-exploration described by Nothdurft et al., 2009). Recent psychophysical observations confirm that such a mixed parallel and serial strategy prevails in difficult visual search contexts over purely serial processes (Guided Search theory, Wolfe et al., 1989; Zenon et al., 2008, 2009a,b). While the LATER model accurately accounts for a purely parallel process, it does not allow for a robust statistical fit of data generated from a mixed parallel/serial strategy. Incorporating an additional parameter, namely an increase in accumulation variance, improves the model's fitting of situations that produce a rotation in the reciprobit plots (**Figures 5** and **6**). However, it remains unable to describe complex situations inducing a combined shift plus rotation of the reciprobit plots, as expected from a mixed strategy involving parallel and serial sub-processes. Very few studies have looked at RT distributions in visual search tasks in humans (Strayer, 1997; Sung, 2008; Reynolds and Miller, 2009; Palmer et al., 2011). Heterogeneity in subjects' strategies has been observed (e.g., **Figures 3–5** in Palmer et al., 2011) but never analysed nor discussed as an intrinsic aspect of visual search underlying sub-processes. We thus posit that, mirroring the individual visual strategies we describe here between our two monkeys, such individual differences also exist in human subjects and might explain some of the discrepancies in the visual search community, especially in experiments involving a very small number of subjects.

The effect of LIP inactivations on mean RT is an increase for the detection of a contralesional target, greater for difficult search conditions that for the easy condition, and no effect for the detection of an ipsilesional target except a decrease in RT variance for Monkey M (Wardak et al., 2004). Because the response to an easily detectable target is almost not affected, these results lead us to propose that LIP is involved in a kind of selection or competition process. What new light does considering the entire RT distribution bring about on the functional consequences of reversible inactivations? We do not observe an overall difference between the easy and the difficult searches. In Monkey M, LIP inactivations affect the detection of both a contra- and an ipsilesional target in different ways. For an ipsilesional target, the RT distributions show a reduced variance. For a contralesional target, the RT distributions show either an increased decisional threshold or a decreased variability combined to a decreased accumulation rate. Monkey G's results suggest the same trend, although our measures fail to reach statistically significance (nearly significant only for the most difficult search condition). From a functional point of view, a decrease in ipsilateral RT variance could correspond to a decrease in the level of noise in a saliency map. Alternatively, it could also correspond to a spatial bias (toward the ipsilesional side of space) narrowing the spatial representation considered for the search. These ipsilateral changes can be expected to have the following contralateral counterparts: (1) a noise increase (possibly correlating with an increased variance) that could lead the perceptual system to adjust the decisional threshold to avoid too many false alarms (we indeed observed more false alarms following LIP inactivations as reported in Wardak et al., 2004) and thus correspond to the swivel interpretation; or (2) after failing to find the target in the narrowed

ipsilesional spatial map (imposing a fixed delay), a shift to search for the target in a narrowed contralesional spatial map, thus resulting in the observation of a shift combined with a rotation of the reciprobit plots. We cannot be more conclusive as both these functional (non-exclusive) hypotheses could fit with the possible roles of LIP in hosting a saliency map (Gottlieb et al., 1998) or participating to perceptual decision-making (Shadlen and Newsome, 1996).

The effects of FEF inactivations on mean RT are an increase for the detection of a contralesional target, equivalent for the three search conditions, and a small increase for the detection of an ipsilesional target for Monkey M (Wardak et al., 2006). Our original interpretation was that FEF inactivations affected the contraversive attentional shifts. The analysis of RT distributions shows very different results for the two monkeys that seem to match their control search strategy. In Monkey M, we observe a shift of the RT reciprobits for a contralesional target. As this monkey seems to analyze the visual scene in parallel, this would correspond to a decrease in the accumulation rate as proposed by the LATER model. This hypothesis would support the suggestion of some authors that FEF, like LIP, hosts a saliency map (Thompson and Bichot, 2005). However, this explanation cannot be generalized to the results of Monkey G. If we now focus on the ipsilateral detection behavior, Monkey M RT distributions are not very affected by FEF inactivations (even if it results in a small change in the mean RT). In contrast, in Monkey G, the reciprobit plots are very different from those of Monkey M, but very similar to contralesional target RT distributions: the general effect of FEF inactivations is an increase in RT variance. This could be due to an increased duration of contraversive attentional shifts. Alternatively, it could also result from an increase in the number of attentional shifts due to a working-memory deficit as has been shown in patients with frontal lesions (e.g., Walker et al., 1998). In addition to this general increased RT variance, these RT distributions also show that, especially for an ipsilesional target, many RTs are faster than in the control condition. A plausible interpretation is that, while contraversive shifts are longer following FEF inactivations, ispsiversive shifts are on the opposite faster. As these ipsilateral shifts can be produced both within the ipsilesional and the contralesional side of space, this could explain the complex shape of the reciprobits. These very short RTs for an ipsilesional target are also observed in an easy feature search condition, producing an early distribution separable from the main RT distribution (**Figure 7**). In the original LATER model, this kind of early distribution has been described as corresponding to express saccades. The fast manual RTs we describe are obviously functionally not equivalent to express saccades, but could correspond, as an alternative interpretation, to faster attentional shifts or a falicitated perception of the ipsilesional targets.

To conclude this section, we cannot propose a single functional mechanism that would be affected by FEF inactivations and explain the entire behavioral results of Monkey M and G, possibly because of their different behavioral strategies. However, our results fit with the proposed role of FEF in attention and perception (e.g., Thompson et al., 2005; Ding and Gold, 2012; also Ibos, Duhamel and Ben Hamed, submitted).

The LATER model we apply to our RT data completely relies on the assumption that the neuronal processes that underlie our behavioral observations follow a pure diffusion model with drift and low variance. Neuronal responses to target detection in the absence or in the presence (visual search task) of distracters are very similar in both the FEF (e.g., Thompson et al., 2005) and LIP (Oristaglio et al., 2006; Balan et al., 2008) and they reflect information accumulation about the presence of the target. However, to our knowledge, there is no report, in these two areas, of noticeable changes in baseline variability between these target detection and visual search conditions nor of baseline changes as a function of visual search difficulty or the number of distracters. The former situation is expected to lead sub-optimal fits by the model, while the latter situation is expected to lead an erroneous threshold change hypothesis. Only direct neuronal recordings can allow us to directly address this point and validate the framework RTs are interpreted in.

In conclusion, this re-analysis of the effect of LIP or FEF inactivations on RTs in a covert visual search task shows that the entire RT distribution contains information worth considering. For example, in Monkey G, the effects of FEF inactivations do not affect the mean RT for detecting an ipsilesional target, whereas their actual effects on the RT distribution is huge. We cannot conclude decisively about the functional mechanisms affected by both LIP and FEF inactivations, because several alternative hypotheses could fit the results. However, what is very clear is that both inactivations have very different effects on the RTs distributions in the two monkeys, much more striking that the subtle differences we already reported on mean RTs. These differences of results between the two monkeys most likely arise from the specific visual search strategy of each animal. Our analyses relied on the LATER model, which has been demonstrated to be a very useful tool to study RTs distributions, thanks to very few parameters. Here, we demonstrate a limitation of this model, in that it does not allow to fit all the behavioral strategies encountered in visual search.

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Insights from neuropsychology: pinpointing the role of the posterior parietal cortex in episodic and working memory

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The role of posterior parietal cortex (PPC) in various forms of memory is a current topic of interest in the broader field of cognitive neuroscience. This large cortical region has been linked with a wide range of mnemonic functions affecting each stage of memory processing: encoding, maintenance, and retrieval. Yet, the precise role of the PPC in memory remains mysterious and controversial. Progress in understanding PPC function will require researchers to incorporate findings in a convergent manner from multiple experimental techniques rather than emphasizing a particular type of data. To facilitate this process, here, we review findings from the human neuropsychological research and examine the consequences to memory following PPC damage. Recent patient-based research findings have investigated two typically disconnected fields: working memory (WM) and episodic memory. The findings from patient participants with unilateral and bilateral PPC lesions performing diverse experimental paradigms are summarized. These findings are then related to findings from other techniques including neurostimulation (TMS and tDCS) and the influential and more abundant functional neuroimaging literature. We then review the strengths and weaknesses of hypotheses proposed to account for PPC function in these forms of memory. Finally, we address what missing evidence is needed to clarify the role(s) of the PPC in memory.

Keywords: parietal lobe, parietal lesion, working memory, episodic memory, autobiographical memory, short-term memory, neuropsychology, source memory

Several years ago the posterior parietal cortex (PPC) stepped into the spotlight as an area of interest in cognitive neuroscience. Traditionally, vague terms such as "association cortex" were used to describe the multiple functions of the PPC. Association cortex referred to the intermediate stage of processing in between primary sensory cortices and frontal areas involved in executive function. The PPC covers a large territory and includes a number of distinct cortical regions including the superior parietal lobule (SPL, BA 7) and the inferior parietal lobule (IPL, BA 39, 40), which includes the angular and supramarginal gyri. Apart from these gross distinctions others propose more detailed parietal parcellations based on analyses of functional and structural connectivity (e.g., Nelson et al., 2010; Uddin et al., 2010; Caspers et al., 2012). Portions of the PPC have been associated with a wide-ranging array of cognitive roles including spatial or selective attention (especially right IPL, reviewed in Chambers and Mattingley, 2005; Husain and Nachev, 2007; Driver et al., 2010; Corbetta and Shulman, 2011), stimulus selection (reviewed in Corbetta and Shulman, 2002), navigation (reviewed in Berthoz, 1997; Postma et al., 2008), visual perception (especially left SPL, IPL: reviewed in Landis, 2000; Berman and Colby, 2009; Pisella et al., 2009), action planning and control (anterior intraparietal sulcus, IPL, SPL; reviewed in Glover, 2004; Tunik et al., 2007; Jax and Coslett, 2009), tool use (IPL: reviewed in Frey, 2008; Arbib et al., 2009), reorienting (IPL: reviewed in Maurizio Corbetta et al., 2008), executive function (SPL, IPL: for a meta-analysis see Niendam et al., 2012), and even general intelligence (SPL, IPL: Gläscher et al., 2010). Clearly, regions of the PPC were considered important for many aspects of cognition, but it had not been linked to memory.

The era of functional magnetic neuroimaging (fMRI) created an opportunity to revisit assumptions regarding brain structure-function links. Of relevance here was the unexpected number of reports in the episodic memory literature that identified PPC activations during memory tasks. In a seminal review paper, Wagner and colleagues reviewed these fMRI findings and presented three plausible roles for PPC involvement in episodic memory (Wagner et al., 2005). The three proposals attention to internal representations, output buffer, and mnemonic accumulator are discussed below. This paper prompted a surge of interest in the PPC/memory relationship as evidenced by 350+ citations since publication.

Thus, research proposing PPC involvement in memory is relatively recent and for many it comes with a large grain of salt. This is in part because neuropsychological patients with PPC damage do not have predominant memory deficits. Instead these patients present with primarily spatial and attentional problems. The complete list of symptoms associated with PPC lesions is highly varied. Damage to the left IPL (angular gyrus) can lead to Gerstmann's syndrome (finger agnosia, left-right confusion,

dyscalculia, dysgraphia), whereas right IPL damage often produces hemispatial neglect, and bilateral IPL damage can result in Balint's syndrome (optic ataxia, optic apraxia, simultanagnosia). It is important to acknowledge one of the caveats of neuropsychological studies is that the lesions themselves do not obey the boundaries between different functional regions within the PPC. This is largely due to the broad vascular territory of the middle cerebral artery over the lateral PPC. Infarcts of the middle cerebral artery reliably damage multiple regions in the PPC. Furthermore, even small lesions may cause damage to neighboring structures in and connected to the lesion site. Therefore it is difficult to find patients with damage isolated to structures solely within the IPL or the SPL. It is also true that researchers do not always have access to clear brain scans and they may not be able to report detailed lesion locations. Consequently, because of this lack of specificity, the more general term PPC is used with regard to patients' lesions unless otherwise noted.

Caveats aside, recent findings suggesting that the predominant symptoms occurring after PPC damage might obscure nuanced memory deficits. This has prompted researchers to revisit this question. Below, I briefly review neuropsychological research investigating episodic memory performance in people with PPC lesions; see **Table 1**. The subsequent section will summarize investigations of working memory (WM). Although episodic and WM are generally addressed separately, they are both included here because both literatures are relatively small, and often patient participants are tested in both domains. More importantly, there is evidence to suggest that both episodic and WM cross-contaminate tasks devoted ostensibly to one or the other (Cowan, 2008). In other words, you often get both episodic and WM contributing to task performance.

This paper updates an earlier review on a similar topic (Olson and Berryhill, 2009) and complements reviews considering PPC activations in episodic memory tasks (Wagner et al., 2005; Rugg and Curran, 2007; Cabeza, 2008; Cabeza et al., 2008; Vilberg and Rugg, 2008; Hutchinson et al., 2009; Uncapher and Wagner, 2009; Shimamura, 2011) and the conflict between the MRI and patient literatures (Schoo et al., 2011).

NEUROIMAGING IDENTIFIES PPC ACTIVATIONS DURING EPISODIC MEMORY

This brief paragraph serves to highlight several observations from neuroimaging data that prompted neuropsychological investigations of episodic memory in people with PPC lesions. Neuroimaging studies first noted that memory tasks reliably elicited PPC activations (e.g., Wojciulik and Kanwisher, 1999; Culham and Kanwisher, 2001). One characteristic pattern of PPC activation in memory studies is known as the parietal old/new effect. This refers to increased activity in the lateral PPC when a participant performing a recognition memory test endorses a stimulus as previously encountered ("old") compared to when the participant rejects a stimulus as novel ("new"), even if their response was incorrect (Kahn et al., 2004; Wheeler and Buckner, 2004; Rugg and Curran, 2007; Kim, 2011). The parietal old/new effect is complemented by a second confidence-related pattern in the PPC. Two dissociable regions respond more robustly to high (inferior IPL) or low (superior IPL) response confidence, again regardless of response accuracy (Kim and Cabeza, 2007, 2009). In both examples, the neural activity in the PPC corresponds to the participant's subjective experience of memory. Other PPC activations reflect response accuracy such that the area in and around the intraparietal sulcus is activated more strongly by correctly remembered items than correctly rejected items (Wagner et al., 2005). Finally, overlapping medial PPC (precuneus) activations are reported during assorted episodic memory tasks tapping associative memory, autobiographical memory and episodic future thinking (reviewed in Addis et al., 2007; Buckner and Carroll, 2007; Cabeza and St. Jacques, 2007; Burgess et al., 2011; for recent findings see also: Burianova et al., 2010; St. Jacques et al., 2011; Addis et al., 2012).

EPISODIC MEMORY AFTER PPC LESIONS

Traditionally, clinicians do not associate memory loss with parietal damage. Indeed, one of the classic texts on PPC function has chapters on visual, tactile, spatial, language, and body-image deficits (Critchley, 1953). Indeed, the well-known British neurologist MacDonald Critchley referred to memory deficits after PPC damage exclusively in terms of impaired spatial imagery (Critchley, 1953). However, there was some indication that patients with parietal damage and hemispatial neglect could have visual (Butters et al., 1970) or auditory memory deficits (Heilman et al., 1974) for stimuli presented in the neglected field contralateral to the lesion. In these studies, stimuli were presented to either the intact or neglected hemifield and after a delay, memory performance was tested. Performance for stimuli presented in the neglected field was worse than for stimuli in the intact field. Verbal WM deficits were also associated with nonspecific left hemisphere damage in patients with aphasia (Warrington et al., 1971; De Renzi and Nichelli, 1975). One difficulty with these earlier findings is the perceptual confound—if a stimulus was not attended due to neglect, performance in memory tasks would also be impaired. Secondly, in many patient-based studies there was a lack of anatomical specificity to describe the location of lesions. Consequently, it remained unclear whether there were any subtle memory deficits associated with PPC damage, *per se*. The increased use of neuroimaging has largely solved the problem of precisely defining the lesion location.

In one more recent case implicating the PPC in episodic memory a closed head injury caused damage to bilateral occipital and the right PPC in a 19-year-old man, patient D.H. (Hunkin et al., 1995). In spite of high-normal intelligence, patient D.H. was able to spontaneously remember only one autobiographical event occurring prior to the accident. Other events had been retold to him, but he claimed that they were not accompanied by a sense that of having personally experienced the events. Semantic information detailing his youth had been relearned and was normal. D.H. did not have anterograde deficits, meaning he had no difficulty retrieving autobiographical events occurring after his accident. In short, his memory deficit was limited to autobiographical events before his brain damage. Deficits in autobiographical memory have been found in several other studies. Davidson and colleagues report the case of patient S.M. who had surgery to remove a tumor in the left parietal lobe

Table 1 | Summary of neuropsychological investigations of non-spatial episodic and working memory.

Authors	Lesion location	Type of memory	Test	Memory deficits
1. Berryhill et al., 2007	Bi PPC (EE555: lateral IPL, angular gyrus; TQ591: L IPL, precuneus, R SPL)	Autobio LTM	AMI, Levine	Spontaneous autobio retrieval
2. Berryhill et al., 2010a	Bi PPC*	Episodic future thinking	Imagine future	Fewer episodic details
3. Davidson et al., 2008	L PPC (lateral, IPL, SPL)	Autobio LTM	Autobio; DRM	Fewer details; Impaired recollection and subjective experience
4. Drowos et al., 2010	Bi PPC*	LTM	Visual/verbal DRM	Fewer false alarms
5. Vuilleumier et al., 2002	R PPC w/neglect (mixed cortical and white matter)	LTM	Object	Impaired explicit memory for contralaterally presented and extinguished items
6. Berryhill and Olson, 2008b	R PPC (IPL and SPL)	WM	Object, location, and conjunction Recognition	Recognition
7. Berryhill and Olson, 2008a	Bi PPC*	WM	Recognition/Recall	Recognition
8. Maldonado et al., 2011	L PPC (IPL)	WM	Unclear	One case of WM impairment after resection
9. Berryhill et al., 2011	*Bi PPC**	*WM/LTM*	*Recognition/Recall*	*Recognition when blocked; Recall when rehearsal was prevented*
PPC PATIENT STUDIES SHOWING INTACT MEMORY				
10. Milner, 1968	*Uni PPC (L, R IPL, SPL)*	*LTM*	*Recognition memory*	*Intact face/pattern memory*
11. Satoh et al., 2011	*R PPC (IPL)*	*LTM*	*Daily memory (Rivermead), Verbal memory*	*Musical anhedonia*
12. Simons et al., 2008	*Uni PPC (L, R, IPL, SPL)*	*LTM*	*Source memory*	*–*
13. Simons et al., 2010	*Uni (L, R, IPL, SPL, Bi PPC*)*	*LTM*	*Source memory*	*Reduced confidence*

For a table of spatial memory deficits please see Olson and Berryhill (2009).

Entries in italics indicate null findings with regard to memory or WM deficits.

*Abbreviations: Bi PPC, bilateral posterior parietal cortex; R, right; L, left; DRM, Deese–Roediger–McDermott (Deese, 1959; Roediger and McDermott, 1995); Autobio, autobiographical memory; LTM, long term memory; AMI, autobiographical memory interview (Kopelman et al., 1989); Levine, Levine autobiographical memory interview (Levine, 2004); *, see Row 1.*

(Davidson et al., 2008). S.M. volunteered that her autobiographical memories did not seem to be accompanied by a sense of having experienced the event herself. However, her memory impairment was broader than that observed in D.H. She was also impaired on the paired-associates subtest of the Wechsler Memory Scale (Wechsler, 1997) and she had low confidence in other memory tasks.

We were able to test two rare patients with bilateral parietal damage in a series of episodic and WM studies, including tests of autobiographical memory. The primary deficit associated with bilateral parietal lesions is simultanagnosia, a component of Balint's syndrome (Balint, 1909). Simultanagnosia is the inability to attend to more than one object at a time. In other words, patients are only able to report the presence of a single item at any moment. Not surprisingly, this piecemeal visual experience renders global percepts of visual scenes impossible. Although both patients had bilateral damage, their lesions were largely non-overlapping. TQ591 had both bilateral IPL and right SPL damage as well as left precuneus involvement and EE555 had more lateral and inferior lesions in the IPL. We administered two autobiographical memory tests (Kopelman et al., 1989; Levine et al., 2002). The first test (Kopelman et al., 1989) emphasized semantic knowledge for different epochs in time, and here the PPC patients performed relatively normally. In the second test (Levine et al., 2002) participants freely recalled events from several time points. These descriptions were followed by a series of specific probe questions to elicit additional details related to each retrieved memory. The two bilateral PPC patients, EE555 and TQ591, were able to freely recall memories, but they were impoverished and significantly lacked details when compared to control participants. However, they performed normally when specific probe questions were provided. This pattern of deficits revealed a dissociation between spontaneous and guided memory retrieval that was inconsistent with a global memory impairment. These data demonstrated that PPC damage impaired patients' abilities to spontaneously and vividly retrieve memories, but absent details could be accessed when memory retrieval cues provided support (Berryhill et al., 2007).

We later tested, whether these two bilateral PPC patients were impaired at describing future events. This type of task is

referred to as "episodic future thinking," or "constructed experience" and it is thought to tap episodic memory retrieval to anticipate the outcome of events yet to happen. Neuroimaging studies of episodic future thinking and autobiographical memory identify overlapping activity in frontoparietal networks (reviewed in Addis et al., 2007; Buckner and Carroll, 2007; Hassabis and Maguire, 2007). We used a paradigm similar to the autobiographical memory paradigm described above (Levine et al., 2002). Verbal prompts cued participants to describe future events (e.g., "Imagine you are meeting a friend for lunch") replicating an approach used with amnesic patients (Hassabis et al., 2007). Performance was measured using text analyses that tallied the numbers of freely reported details. There were also measures of subjective experience in which participants were asked to rate how present and salient the imagined events felt and the overall quality of the conjured experienced. Our results showed that the two bilateral PPC patients were impaired in their ability to envision richly detailed future events (Berryhill et al., 2010a). More precisely, the bilateral PPC patients' responses were significantly lower than those of controls for measures of spatial integration and overall quality. Somewhat surprisingly, given previous indications that PPC lesions can reduce a sense of subjective experience, the bilateral PPC patients did not rate their sense of presence or salience significantly lower than healthy controls. Here, again, was evidence of a restricted deficit in episodic memory. Constructed experience has been evaluated in at least one other patient group with parietal-area damage. Patient participants with diffuse axonal injury were tested on constructed memory and this performance was correlated with damaged areas as identified through diffusion tensor imaging (Kondo et al., 2010). In these patients PPC damage (inferior IPL) correlated with performance on the constructed memory task (Kondo et al., 2010).

The autobiographical and constructed experience findings from the patients with bilateral PPC lesions used similar free recall paradigms with similar advantages. One advantage was to minimize encoding demands since the events occurred prior to the lesions or could be assembled collage-style from premorbid occurrences. A second advantage of these studies was that the instructions were simple and judging from the length of transcripts, people enjoyed participating. Drawbacks of these studies are that scoring requiring a text analysis that is enormously time consuming and requires some level of rater subjectivity, and the bulk of the episodic memory field uses more standardized experimental paradigms. Below, we review the findings from more commonly used experimental paradigms. Two papers used the Deese–Roediger–McDermott (DRM) (Deese, 1959; Roediger and McDermott, 1995) false-memory paradigm to test patient participants with PPC damage (Davidson et al., 2008; Drowos et al., 2010). In the DRM paradigm, lists of semantically related items are presented (e.g., pillow, night, blanket). Next, participants perform a delayed memory recognition task in which they make old/new judgments and for old responses they make a remember/know judgment reflecting whether there was a clear recollection or a sense of familiarity for the stimulus. The essential finding is that there is a high false alarm rate to new lure items that are closely related to a stimulus list (e.g., sleep). The aforementioned patient S.M. performed abnormally, when compared to control participants by having lower recognition accuracy and reduced recollection as indicated by significantly fewer remember responses (Davidson et al., 2008). Her performance also reflected fewer false alarms to the lure words. We also tested patients EE555 and TQ591 using the visual and verbal versions of the DRM paradigm (Drowos et al., 2010). As with patient S.M., the bilateral PPC patients performed abnormally from control participants by committing fewer false alarms to lure words and by making fewer remember responses to the false alarms they did make. However, when we used visual stimuli instead of verbal stimuli, a different pattern emerged. Visual DRM studies do not tend to have the degree of false memories because of the "distinctiveness heuristic" rendering visually presented stimuli more distinctive (e.g., Israel and Schacter, 1997). If the PPC damage impaired gist perception due to a deficit in recollection, as proposed by Davidson et al. (2008) we should have seen the same pattern for auditory or visual versions of the DRM. The bilateral PPC patients performed more accurately in the visual DRM. However, EE555 was unable to take advantage of the distinctiveness heuristic and she maintained the same level of false memories across both versions of the DRM. EE555's remember/know responses support the idea that she was less confident in her memory, though, as she made only a few remember responses. It is also important to note that the bilateral PPC patients did not have a general problem with gist information. They performed normally when recounting the thematic memory for short stories, although again, they reported fewer details than control participants (Drowos et al., 2010).

Memory impairment for learning paired-associates has been tested in unilateral and bilateral PPC patient populations (Davidson et al., 2008; Berryhill et al., 2009). In a set of three paired-associates experiments testing the bilateral PPC patients, we found that they were not impaired on the memory retrieval aspect of a word pair task (Giovanello et al., 2006), linking variable amounts of information with items in a fan task (Radvansky, 2005), or at learning audio/visual pairs. In the word pairs and audio/visual pairs tasks response confidence was measured in two different ways: using the remember/know procedure and as a numeric (1–6) rating, respectively. The PPC patients' numeric confidence ratings were significantly lower than the control participants in the audio/visual task, but the number of remember responses was no different from controls in the word pairs experiment (Berryhill et al., 2009). We concluded that the PPC patients had reduced confidence in their responses.

Several researchers have conducted investigations looking at source memory, the ability to retrieve specific details of the encoding stage. For example, a source memory task may require you to remember whether you heard the news on the radio or on the television. There are several findings reporting normal source memory in patients with PPC damage (Ally et al., 2008; Simons et al., 2008, 2010). First, Simons and colleagues selected participants with unilateral parietal damage in areas that overlap with fMRI brain activations observed during source memory tasks (Simons et al., 2008; for relevant findings see also Duarte et al., 2011). At encoding, participants were shown words or pictures and for each item they were asked to judge whether the item was pleasant/unpleasant or from entertainment/politics. At test, participants had to remember which judgment they had made for

each stimulus. The patients performed normally on the source memory judgment. Subsequently, Simons et al. (2010) conducted a series of three source memory tasks in unilateral and bilateral PPC patients (including bilateral PPC patients EE555 and TQ591). Here, participants heard sentences presented in a male or female voice. At test, they indicated whether the sentence was old or new, rated their confidence and then judged whether the original voice had been male or female and finally, how confident they were in their response. All participants and patients performed the old/new recognition task normally and had normal confidence ratings. There were no group differences in the source judgment task either. However, the bilateral PPC patients had significantly lower confidence in their source judgments. A follow-up experiment using visual stimuli found the same dissociation between normal source memory accuracy accompanied by impaired confidence. Davidson et al. (2008) found a similar dissociation in patients with unilateral PPC damage. He presented words with definitions in visual or auditory domains and later asked participants to retrieve the sensory domain at encoding and to make remember or know responses. While the patients performed accurately when performing the source memory judgment, they made significantly fewer remember responses. This is evidence that recollection confidence declines after PPC damage.

One last study tested both unilateral right and left PPC patients in a recognition memory paradigm. Haramati et al. (2008) presented participants with pictures, sounds, and words and asked for preference ratings at encoding. Later, participants performed a delayed recognition test. Only the right PPC patients had any deficits, and these were limited to poor recognition for pictures and sounds, but not words (Haramati et al., 2008). Tempering this finding were voxel-based analyses of lesion location and performance suggested that the overlap in right frontal regions, rather than parietal cortex, predicted memory deficits.

ROLE OF THE PPC IN EPISODIC MEMORY

The above findings present nuanced rather than global memory deficits. Where medial temporal lobe amnesics have dramatic memory impairments, PPC patients have modest deficits. The data described above has been used to support several different mechanisms of PPC involvement in episodic memory. Wagner et al. (2005) described three separate proposals, attention to internal representations, output buffer, mnemonic accumulator, that have been very helpful springboards for neuropsychological researchers. A fourth proposal is the cortical binding of relational activity (CoBRA) theory (Shimamura, 2011). Finally, Davidson et al. (2008) developed an alternative view, the subjective experience hypothesis. These views are discussed below.

ATTENTION TO INTERNAL REPRESENTATIONS

The initial proposal implicated the PPC in directing attention to the mental representation of a memory. A related elaboration, the attention to internal memory (AtoM: Cabeza, 2008; Cabeza et al., 2008) proposed a distinction between spontaneously retrieved memories and deliberately sought memories akin to the distinction between bottom-up and top-down attention. Here, the proposal identifies the role of the IPL is involved in bottom-up guided, spontaneous retrieval, whereas the SPL is responsible for top-down directed, effortful retrieval. This view accounts for findings in PPC patients with more inferior lesions who show normal performance when memory cues are provided (intact top-down retrieval) and impaired performance when they must retrieve the memory on their own (impaired bottom-up retrieval). This perspective has been criticized in a large fMRI meta-analysis that failed to reveal an inferior/superior subdivision based on whether the retrieval event was mediated by top-down or bottom-up attention (Hutchinson et al., 2009). However, at least one fMRI finding identifies IPL activations during bottom-up retrieval of a paired associate and SPL activations during top-down retrieval. Furthermore, these neuroimaging findings extended to PPC patients with IPL and SPL lesions (Ciaramelli et al., 2010).

EPISODIC OR OUTPUT BUFFER

This explanation proposes that the PPC serves as one module within the multimodal model of memory called the episodic buffer (Baddeley, 2000). The episodic buffer is hypothesized to maintain sensory and mnemonic information in a common "language" or representation. It may serve as a sort of Esperanto for the brain. The information in the buffer is thus available for manipulation and is closely related to WM function. This view cannot account for the finding that associative memory for audio/visual pairs remains intact (Berryhill et al., 2009), because multimodal storage is necessary for these types of tasks. Secondly, this explanation predicts that PPC patients should have poor performance in tasks asking for narrative structure, such as the autobiographical or constructed experience tasks (Berryhill et al., 2007, 2010a). However, although lacking rich details, the patients provide accounts with intact and appropriate narrative structure.

MNEMONIC ACCUMULATOR

This proposal suggests that PPC neurons register an index signaling memory retrieval status and that when this index passes threshold, participants would endorse an item as old. In other words, this proposal endows the PPC with the ability to measure memory strength. A prediction of this hypothesis is that memory decision-making would be impaired after PPC damage. However, PPC patients do not have *general* memory deficits as would be predicted if they had difficulty interpreting a missing or damaged index of memory strength. Instead the deficits that emerge tend to relate to memory confidence even when memory accuracy is intact (Haramati et al., 2008; Berryhill et al., 2009; Drowos et al., 2010).

CORTICAL BINDING OF RELATIONAL ACTIVITY (CoBRA)

Shimamura recently proposed that the ventral PPC interacts with the prefrontal cortex and medial temporal lobe and creates a cortical network of the details related to an episodic memory (Shimamura, 2011). According to CoBRA, medial temporal lobe regions form associations at encoding, but through consolidation the vPPC becomes more important for reactivating, or to use their term "re-collecting," the ensemble of relevant episodic details. CoBRA predicts that there should be greater vPPC activity when memories contain greater multimodal details because their retrieval requires more cross-cortical

links of feature information. A second prediction is that the vPPC should be more involved when the retrieval process relies more on recollection than familiarity. A potential challenge for CoBRA is the finding that patients with PPC lesions perform normally at source memory tasks (Simons et al., 2008, 2010). However, Shimamura suggests that these types of source memory tasks may not be sufficiently multimodal to require vPPC activity. A second potential problem is that patients with bilateral parietal damage perform normally at associative learning tasks even those that require multimodal pairings (Berryhill et al., 2009).

SUBJECTIVE EXPERIENCE

This view puts forth the idea that the PPC signals the perceived oldness of an event. In essence, this distinguishes between something vividly retrieved versus something vaguely recalled. Proponents suggest that damage to this processing explains findings of reduced confidence in PPC patients' memories across various paradigms (Hunkin et al., 1995; Ally et al., 2008; Davidson et al., 2008; Berryhill et al., 2009; Drowos et al., 2010; Simons et al., 2010). However, reduced memory confidence is not universal and the subjective experience account does not currently predict why some memory tasks are accompanied by reduced memory and others are not.

Our own view has been to create a hybrid of two existing proposals: the subjective experience and attention to internal representations (Berryhill et al., 2009; Drowos et al., 2010). The advantage for this merger is that it includes a role for the PPC in strategically accessing and attending to the full set of details associated with a particular event. It also includes the function of assessing the vivid richness of memories to account for the deficits in memory confidence. In other words, when the PPC is damaged, patients may not be able to fully reactivate the full assembly of stored details to revivify the event. This would lead to impoverished recollections and a reduced sense of re-experiencing a past event.

PPC AND WORKING MEMORY

In cognition, WM is a core executive function that allows us to maintain information over short delays. Neurophysiological data provided the first indications that neurons in the PPC were involved in maintaining WM representations. Recordings from non-human primates indicated that PPC neurons, in addition to the prefrontal cortex, maintained their activity after during the delay period when there were no stimuli available (e.g., Chafee and Goldman-Rakic, 1998, reviewed in Constantinidis and Procyk, 2004; Rawley and Constantinidis, 2009; for work in rodents see review by Bucci, 2009).

It may strike some as disjointed to pair episodic memory with WM given the fact that these two topics reside in different literatures. Others make the case quite clearly that it is difficult to develop tasks that precisely test episodic or WM alone (Cowan, 2008). In disentangling the interplay of medial temporal, prefrontal, and PPC structures in various forms of memory, it is important to look at WM. The traditional division between episodic and WM was established by classic neuropsychological research in medial temporal lobe amnesia patients (e.g., Scoville and Milner, 1957). However, recent findings suggests that amnesics have abnormal WM performance even at short delay intervals (Warrington and Taylor, 1973; Ryan and Cohen, 2004; Ranganath and D'Esposito, 2005; Hannula et al., 2006; Olson et al., 2006a,b; Ezzyat and Olson, 2008; but see Baddeley et al., 2010). For example, medial temporal lobe amnesic patients were less accurate and slower when remembering a single face over a 1 s delay interval (Ezzyat and Olson, 2008). These findings point toward greater interactions between episodic memory and WM than was previously appreciated (see also: Ranganath et al., 2005; Jonides et al., 2008; Graham et al., 2010).

In addition, a series of high-impact findings in the fMRI literature indicated that PPC activations reflected the number of items maintained in WM (Todd and Marois, 2004, 2005; Xu and Chun, 2005). In these studies, the IPL, specifically the intraparietal sulcus, showed parametric increases in activity up to the behavioral WM capacity limit. In the ERP literature, a similar finding, the contralateral delay activity, also underscored the importance of posterior regions in WM maintenance (reviewed in Drew et al., 2006). The prediction from these neuroimaging data was clear: PPC damage should lead to WM deficits.

PPC DAMAGE AND WM

The majority of WM studies in neuropsychological patients with PPC lesions test performance in spatial WM tasks. This is due to the association of parietal cortex with spatial attention. Spatial WM impairments have been reported in patients after lesions to the right hemisphere (De Renzi and Nichelli, 1975; De Renzi et al., 1977; Hanley et al., 1991; Kessels et al., 2000; Postma et al., 2000), left PPC (Baldo and Dronkers, 2006), and right PPC (Husain et al., 2001; Malhotra et al., 2004, 2005, 2009; Pisella et al., 2004; Ravizza et al., 2005; Finke et al., 2006). As noted previously, earlier neuropsychological studies were unable to provide more detail regarding the anatomical boundaries of their patients' lesions due to a lack of brain imaging. A number of these studies tested spatial WM using the Corsi block-tapping task (Corsi, 1972) in which participants echo a sequence of taps across different locations as demonstrated by the experimenter (see Olson and Berryhill, 2009 for a summary of the spatial WM findings).

A few reports using other paradigms confirm a spatial WM deficit following right PPC damage. For example, in a population of unilateral right PPC patients with hemispatial neglect, WM deficits were observed across eye movements (Vuilleumier et al., 2007). The patient participants were impaired at remembering the spatial arrangement of stimuli in a spatial WM task where participants judged the location of a single target across a 2–3 s delay. When the task required eye movements during the delay period, a spatial WM deficit emerged only when gaze was redirected from left (neglected hemifield) to right (intact hemifield).

Other reports using different paradigms confirmed that WM could be impaired in patients with unilateral right PPC lesions who did not have neglect. In a series of tasks testing spatial, object and spatial-object conjunction WM, patients with right PPC lesions demonstrated a general WM deficit across spatial and non-spatial WM tasks (Berryhill and Olson, 2008b; but see Pisella et al., 2004). WM was tested using a recognition

paradigm in which a probe image appeared after the maintenance period and participants judged whether the probe had appeared in the memory set or whether it was new. The manner by which WM was tested proved to be important. When object or order WM was tested using recognition bilateral PPC patients replicated the general WM deficit, but when WM was tested using recall, WM performance was normal (Berryhill and Olson, 2008a). This pattern of behavior extended beyond visual WM to aurally presented verbal stimuli (Berryhill et al., 2011). These findings seemed to point strongly toward PPC involvement in WM retrieval, since the WM deficits were associated with recognition rather than recall performance. However, these studies had used separate blocks of recall and recognition WM trials. The separation of tasks had been deliberate to keep the instructions simple. When recall and recognition trials were intermingled so that the retrieval demands were unpredictable, the bilateral PPC patients performed normally in both WM tasks (Berryhill et al., 2011). These data showed that the PPC damage did not eliminate the ability to make recognition WM judgments, but it did do something to patients' recognition performance when they knew they were going to be asked to make recognition judgments.

The distinction between recall and recognition WM performance may also guide the interpretation of several other findings in patients with bilateral PPC damage. First, two patients with bilateral PPC damage were able to accurately name the type of biological motion shown in point-light displays (Huberle et al., 2009). We also observed accurate identification of biological motion using point-light displays in EE555 (Berryhill and Olson, unpublished observations). This observation indicates that bilateral PPC damage does not entirely eliminate the ability to integrate multiple objects over time and argues against a general WM deficit. Since naming point-light displays requires recall responses, these findings are consistent with the successful performance on the recall WM tasks described above. Second, in a series of verbal whole report WM experiments, patient GK showed that he was able to recall more than a single item, but he required a significantly greater amount of time to perform WM tasks and to process information in general (Duncan et al., 2003). These authors interpreted their findings in terms of the Theory of Visual Attention (Bundesen, 1990; Bundesen et al., 2005, 2011) to suggest that the primary deficit was in processing speed. Although patients frequently require more time to process information it does not explain the difference in performance between recall and recognition WM trials. Finally, several papers have tested the importance of spatial factors in PPC patients' performance. The spatial separation between local elements in Navon letter stimuli modulates patients' performance such that they do better at identifying the global letter when the local items are closer together (Huberle and Karnath, 2006) or when the stimuli bias processing to intact parvocellular responses along the ventral visual stream (Thomas et al., 2012). Control participants perform similarly to bilateral PPC patients when their gaze was restricted (Dalrymple et al., 2010). These last findings provide added evidence that WM deficits after PPC lesions are subtle. This highlights the question of determining what the role of the PPC in WM might be.

One recent paper attempted to answer this question by examining WM deficits as a function of PPC subregion. Nature does not follow anatomical boundaries in lesion patients, which makes it difficult to parse anatomical distinctions. However, Koenigs et al. (2009) tested WM in a large number of patients with superior PPC or no superior PPC damage. They tested these populations on subcomponents of the Wechsler Memory scale (Wechsler, 1997). They found that damage to the SPL was impaired specifically when the tasks demanded manipulation rather than passive maintenance. For example, they found that WM performance was normal in the forward digit span task but abnormal in the backward digit span task (Koenigs et al., 2009). These findings serve as an important start in matching the more specific clusters of activity reported in fMRI findings with the disparate PPC damage in patient findings.

ROLE OF THE PPC IN WM

There are several hypothesized roles for PPC involvement in WM. The nature of these views is strongly shaped by the weighting of the data from the researcher's experimental approach. In other words, the starting point of the investigators influences the set of findings they emphasize. In a previous review, we described three proposals: information manipulation, information load and retrieval process (Olson and Berryhill, 2009). These views will be briefly noted below with the addition of a new proposal, the internal attention hypothesis.

INFORMATION MANIPULATION

One possibility is that the PPC, in particular the SPL is involved in manipulating information stored in WM. Several neuroimaging studies report increased superior parietal activations only when manipulation is required. Tasks requiring this kind of manipulation include spatially reordering stimuli based on cues (Wendelken, 2008), reordering the sequence of stimuli (Marshuetz et al., 2000; Wager and Smith, 2003; Marshuetz and Smith, 2006), or performing mental mathematical calculations (Dehaene et al., 1999, 2004). Additional support for this view comes from recent neuropsychological data showing impaired WM in patients with superior PPC damage only (Koenigs et al., 2009). The TMS literature provides complementary evidence with data showing that stimulation to superior PPC regions does not disrupt performance in a simple spatial WM task (recall or recognition), whereas TMS to the dorsolateral prefrontal cortex did impair WM (Hamidi et al., 2009). Several groups have reported that stimulating the superior PPC, particularly the right parietal lobe, improves reaction times in spatial WM tasks (Hamidi et al., 2008; Yamanaka et al., 2009).

One criticism of the information manipulation hypothesis is that PPC activations are observed in fMRI studies of WM tasks without manipulation demands (e.g., Todd and Marois, 2004, 2005; Xu and Chun, 2005, 2007; Schluppeck, 2006; Xu, 2007). This raises the question of the relationship between fMRI and other experimental techniques. A second criticism is that some sources of evidence seem to show TMS effects in WM tasks that do not require information manipulation, for example TMS speeding reaction times after SPL stimulation in simple WM

tasks (Hamidi et al., 2008). However, it is important to note that depending on the paradigm, TMS may be facilitatory or inhibitory.

PURE STORAGE AND RETRIEVAL PROCESS HYPOTHESES

The finding that the WM retrieval task, recall or recognition, predicted intact, or impaired WM performance is inconsistent with the information load interpretation (Berryhill and Olson, 2008a; Berryhill et al., 2011; see also Berryhill et al., 2010b). This pattern was observed across several visual stimulus sets (tools, color patches, novel shapes, colorized Snodgrass drawings) (Berryhill and Olson, 2008a,b) and verbal stimuli (auditory words) (Berryhill et al., 2011). In each case the WM maintenance demands were the same, yet the performance differed. These data led us to propose PPC involvement in WM retrieval (Berryhill and Olson, 2008a,b; Olson and Berryhill, 2009). This explanation had the added benefit of fitting well with patients' selective deficits in episodic memory (Berryhill et al., 2007, 2011). This appealingly parsimonious explanation is no longer able to account for all of the neuropsychological findings and we have moved toward an internal attention account, described below.

INTERNAL ATTENTION

Unpredictable retrieval demands restore WM performance on recognition tasks in patients with bilateral PPC lesions (Berryhill et al., 2011). What explains the previous findings showing WM deficits for WM trials probed by recognition (Berryhill and Olson, 2008a; Berryhill et al., 2011)? We suspected that it had to do with differences in strategy when trials were intermingled rather than in separate blocks of recognition and recall WM trials. Accordingly, one role of the PPC, specifically bilateral IPL, is to maintain attention on items in WM to keep these representations from decaying. This process, sometimes referred to as *attentional refreshing,* refers to a recycling in and out of the attentional focus (Cowan, 1999; Chein, 2003; Barrouillet and Camos, 2009; Bledowski et al., 2009; Lewandowsky et al., 2009; Chein and Fiez, 2010). Importantly, this process is hypothesized to occur as a default material-general process, meaning it will update information currently in the focus of attention. When the focus of attention shifts to another item in WM items will begin to decay until the item returns to the focus. In addition there are active material-specific processes, such as the visuospatial buffer and phonological loop that maintain items in WM. Thus, during recall or interleaved blocks of trials, the material-specific maintenance mechanisms successfully support WM performance in patients with PPC damage presumably due to reliance on intact frontal structures. However, when there are blocks of recognition trials, PPC disruption caused by brain damage (Berryhill and Olson, 2008a,b; Berryhill et al., 2011) or tDCS (P4 stimulation) (Berryhill et al., 2010b) prevents successful attentional refreshing. Recent neuroimaging supports the view that strategy influences encoding related activations in frontoparietal regions at least in change detection tasks (Linke et al., 2011). Because participants have relied on this WM maintenance strategy and failed to supplement it with material-specific processes, their WM performance suffers.

This hypothesis makes the prediction that WM tasks requiring recall responses should not rely on the PPC whereas WM tasks requiring recognition responses should rely on PPC activity. There is some fMRI evidence supporting this prediction. The PPC is selectively activated during WM tasks probed by recognition but not during those probed by recall (Chein and Fiez, 2001, 2010; Chein et al., 2011). In these studies, Chein and colleagues are some of the few researchers to compare activity across different WM retrieval demands. Their data show that the SPL responds in a domain-general way such that it is strongly activated during verbal or spatial WM tasks during the encoding, maintenance and coordination phases. In short, the PPC is involved in a strategic manner during WM tasks. However, further work is needed to clarify the relative contributions of IPL and SPL regions to WM.

CHALLENGES AND CONTINUATION

The present review examined deficits in episodic memory and WM after PPC damage. Of course, it is important to remember that the neuropsychological approach has a series of limitations. As noted in the introduction, patient participants have lesions that damage multiple brain regions and subregions of the PPC. The lack of specificity in documenting structure-function associations is certain to be frustrating to researchers accustomed to other research methods such as fMRI. The cross-region lesion becomes more difficult to interpret as more functional subdivisions of the PPC are identified by newer techniques such as resting state and functional connectivity (Vincent et al., 2006, 2008; Nelson et al., 2010; Uddin et al., 2010; Zhang and Li, 2012) and dynamic causal modeling (Ma et al., 2011). These techniques also provide a new way of evaluating training regimes by evaluating changes in connectivity after training (Takeuchi et al., 2010). The resolution to differences between the fMRI and neuropsychological realm may be best addressed using neurostimulation techniques to temporarily lesion specific subregions of the larger PPC territory.

A second area where neuropsychology is silent is the phase or timecourse of PPC involvement. There are a number of experiments investigating PPC contributions during each phase(s) of memory (encoding, maintenance, or retrieval). Recent findings investigating episodic memory explore involvement during the phases of encoding (Wimber et al., 2010; Uncapher et al., 2011), maintenance (Buchsbaum et al., 2011), and retrieval (Xue et al., 2010; Seibert et al., 2011; Sestieri et al., 2011). Related findings exist for WM encoding (Tseng et al., 2010; Linke et al., 2011; Ravizza et al., 2011), maintenance (Todd and Marois, 2004; Xu and Chun, 2005; Ikkai and Curtis, 2011; Lepsien et al., 2011), and retrieval (Oztekin et al., 2009). Further advances from neurophysiology highlight additional factors such as the hemifield in determining WM capacity and fidelity (Buschman et al., 2011). Again, neurostimulation may be key to disentangling the temporal aspects of PPC involvement in various forms of memory while avoiding concerns related to cortical reorganization. Furthermore, patient participants may be in poor general health or on medications that affect cognition. Yet, in spite of these limitations, the neuropsychological approach is a powerful tool that raises provocative questions. Undoubtedly, recent and future

findings using diffusion tensor imaging, functional connectivity, dynamic causal modeling, neurostimulation, even genetics, as well as fMRI and EEG, will prompt new questions to investigate in patient populations. In this sense it remains "early days" in understanding PPC contributions memory.

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Towards an understanding of parietal mnemonic processes: some conceptual guideposts

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The posterior parietal lobes have been implicated in a range of episodic memory retrieval tasks, but the nature of parietal contributions to remembering remains unclear. In an attempt to identify fruitful avenues of further research, several heuristic questions about parietal mnemonic activations are considered in light of recent empirical findings: Do such parietal activations reflect memory processes, or their contents? Do they precede, follow, or co-occur with retrieval? What can we learn from their pattern of lateralization? Do they index access to episodic representations, or the feeling of remembering? Are parietal activations graded by memory strength, quantity of retrieved information, or the type of retrieval? How do memory-related activations map onto functional parcellation of parietal lobes suggested by other cognitive phenomena? Consideration of these questions can promote understanding of the relationship between parietal mnemonic effects and perceptual, attentional, and action-oriented cognitive processes.

Keywords: memory, parietal, fMRI, EEG, retrieval, recollection, familiarity, attention

TOWARDS AN UNDERSTANDING OF PARIETAL MNEMONIC PROCESSES: CONCEPTUAL QUESTIONS

A host of recent neuroimaging studies have documented the activation of areas of the posterior parietal cortex (PPC) during episodic memory retrieval (reviewed, *inter alia*, by Wagner et al., 2005; Skinner and Fernandez, 2007; Hutchinson et al., 2009; Spaniol et al., 2009; Kim, 2012). These findings converge with earlier electrophysiological studies that had reported event-related potentials recorded over parietal scalp that index episodic recognition (reviewed by Friedman and Johnson, 2000; Mecklinger, 2000; Rugg and Curran, 2007). One upshot of those neuroimaging studies is that medial parietal regions, including retrosplenial cortex, the precuneus, and posterior cingulate cortex, which are strongly interconnected with medial temporal lobe regions (Kahn et al., 2008), are activated in retrieval tasks; this accords with earlier clinical findings that damage to medial parietal areas may yield "retrosplenial amnesia" (Valenstein et al., 1987), a diagnostic category that should be understood as referring to memory impairments resulting from damage to the medial parietal regions in general (Aggleton, 2010). This interconnection has been more recently understood in light of all these areas forming part of the default mode network (DMN) (Raichle et al., 2001), which will be discussed below. Slightly more surprising in light of conventional neuropsychological wisdom were the reports of lateral parietal mnemonic activations. It is still unclear whether neuropsychological findings (e.g., Berryhill et al., 2007, 2009; Haramati et al., 2008; Simons et al., 2008, 2010; Schoo et al., 2011), are in consonance with the implication by neuroimaging of the parietal cortex in mnemonic processes, as lateral parietal damage does not seem to cause significant mnemonic impairments. However, even if intact lateral parietal cortices are not absolutely necessary for retrieval success, the nature of the lateral parietal activations engendered in connection with remembering is in need of explication. A number of explanations of lateral parietal mnemonic functions have been offered, but no single account offered to date seems to successfully explain the full range of empirical evidence, from a variety of paradigms, regarding this issue.

In the present article, I would like to examine several conceptual questions regarding relationships between memory, perception, attention, and action that are raised or emphasized by the parietal mnemonic issue, focusing specifically on findings regarding lateral parietal cortices. Several detailed scholarly reviews and meta-analyses of relevant studies have recently been published (e.g., Hutchinson et al., 2009; Uncapher and Wagner, 2009; Schoo et al., 2011; Kim, 2012), providing a database of findings upon which I will rely in framing the issues under examination. What follows is far from exhaustive, and reflects a mid-course effort to put some parts of the parietal mnemonic literature into a framework that might inform future empirical studies. At the risk of oversimplification, it might be heuristically helpful to consider the parietal mnemonic issue in light of a mosaic of several basic questions. These are: Do parietal mnemonic activations reflect memory processes, or the representation of the contents of memory? Are they indicative of pre-retrieval, retrieval, or post-retrieval processes? Are they related to the veridicality of memory? Are they primarily modulated by strength, quality (e.g., item vs. source), or quantity of retrieved information? Are they fundamentally lateralized or bilateral in nature? Do they represent parietal regions' membership in cognitive control, selective attention, or DMNs? In the following sections we will address these questions.

PROCESSES OR CONTENTS?

Do mnemonically related activations indicate that lateral parietal cortices are loci of stored representations, or are they a substrate of intrinsic or ancillary retrieval processes? Current accounts of parietal mnemonic function may be categorized by how they

answer that question. As the parietal areas that have been implicated in retrieval processes consist of a number of cytoarchitectonic and functional areas, multiple mnemonic functions are possible according to each account. The *Mnemonic Accumulator* model (Wagner et al., 2005; Donaldson et al., 2010) suggests that parietal activations during retrieval reflect the accumulation of a match signal between a recognition probe and representations stored elsewhere in the brain. The probe is judged to be old if that accumulated signal exceeds a certain threshold. Therefore, in this view, parietal mnemonic activations reflect processes intrinsic to retrieval. However, such signal accumulation is also posited to be part of perceptual judgment processes (Ploran et al., 2007), so the function is not specifically mnemonic. A related proposal is that inferior lateral parietal activation reflects expectations regarding the mnemonic status of a presented item, rather than sensitivity to the strength of a mnemonic trace (O'Connor et al., 2010; Buchsbaum et al., 2011). This *Expectation* approach, too, is a process function account.

The *Attention-to-Memory (AtoM)* account (Cabeza et al., 2008, 2011; Ciaramelli et al., 2008, 2010) explains parietal activations as reflecting attentional processes ancillary to retrieval: either top-down attention to cues preceding retrieval, or bottom-up capture of attention by retrieval output or the retrieval cue. In this account, activity in superior parietal cortices, ranging from the intraparietal sulcus (IPS) up to superior medial parietal regions, roughly the area of Brodmann Area (BA) 7, is posited to reflect top-down focal attention especially important for challenging retrieval tasks, while anterior inferior lateral parietal activations (in the vicinity of the supramarginal gyrus, overlapping BA 40) is explained as reflecting bottom-up capture of attention by easily accessed rich memoranda (Cabeza et al., 2008, 2011). In other words, this is a process account, but one that posits that the activations represent processes that are not intrinsically mnemonic.

In contrast to that attentional focus, posterior inferior parietal cortex in the vicinity of the angular gyrus (AG; BA 39) is not an area that has been implicated in attention systems, and therefore seems to require a different account—such as the *Cortical Binding of Relational Activation* (*CoBRA*) hypothesis (Shimamura, 2011; a related proposal is found in Vilberg and Rugg, 2008b), which focuses specifically on that region. In that model, ventral parietal cortex in the vicinity of AG is said to provide a stable substrate of representation for consolidated higher-level perceptual information—a content function.

Finally, in the *Output Buffer* (Vilberg and Rugg, 2007, 2008a,b, 2009; Guerin and Miller, 2011) and the *Memory-to-Action* models, (Haramati et al., 2008), ventral parietal areas are postulated to support temporary post-retrieval representations. The *Output Buffer* account, based on a similar role played by the Episodic Buffer, a proposed component of working memory (Baddeley, 2000), posits that left lateral inferior parietal cortex supports the representation or maintenance of retrieved episodic information—a content function. Proponents of this view (Vilberg and Rugg, 2009) complement the proposal by suggesting that more dorsal activations, especially in the middle (horizontal) segment of the left IPS, is responsive to the relative salience of retrieval cues associated with target information—a process function. The *Memory-to-Action* model (Haramati et al., 2008) is an extension of the *Output Buffer* model. Inspired by findings that extensive left ventral parietal lesions caused no impairment on recognition tasks that had yielded robust activations in those same areas, it postulates that ventral parietal areas are primarily important for maintenance of retrieved episodic information, in a format amenable to additional processing to guide subsequent behavior—a post-retrieval content function. In contrast to other models, the Memory-to-Action hypothesis postulates that ventral parietal activations represent post-retrieval processes exclusively, and therefore predicts that lesions in the areas identified by neuroimaging studies will not yield retrieval deficits *per se*, but may yield deficits in subsequent processing utilizing the retrieved information.

Among the process-focused accounts, the *Accumulator* account (Wagner et al., 2005; Donaldson et al., 2010) is based on a ramified model of recognition memory (Ratcliff, 1978; Ratcliff and Starns, 2009), and evidence that posterior parietal areas serve an accumulator function in perceptual decision-making (Ploran et al., 2007). What is said to be accumulated is a signal indicating "the amount of evidence that retrieval cue corresponds to a studied item" (e.g., Okada et al., 2012). However, this account seems to limit the parietal role in ecphory to recognition. Similarly, the *Expectation* account (O'Connor et al., 2010; Buchsbaum et al., 2011), which focuses on violation and confirmation of the mnemonic strength of the probe, would seem to be specific to the recognition process. This is problematic, as lateral parietal areas seem to be implicated in cued recall no less than in recognition. Because of methodological reasons, the majority of studies of parietal mnemonic function have employed recognition as the memory assay. However, cued recall studies extant in the literature (e.g., Allan and Rugg, 1997; de Zubicaray et al., 2007; Seibert et al., 2011a,b; Hayama et al., 2012; Okada et al., 2012) indicate that similar activations are found under those conditions as in recognition; we have recently confirmed that finding in an electroencephalographic (EEG) study of cued recall of cross-modal and unimodal pair associate learning (Levy, unpublished data). Since in successful cued recall there is no probe to be recognized (there is a cue, but in principle it may be stipulated to be old, and no judgment is made on it), accumulation of a probe-representation match signal is not task-relevant for retrieval success. Even if recognition of the probe does occur automatically, that is insufficient to successfully recall the target information. Such findings challenge the *Accumulator* and *Expectation* hypotheses. It has recently been proposed that the accumulator function should be assigned to mid-IPS regions (Suzuki et al., 2011; Okada et al., 2012), or more generally to dorsal parietal regions in BA 40 (Huijbers et al., 2010). Accordingly, the signal accumulation process and its IPS substrate might theoretically be partially dissociated from recollective and cued recall processes that lead to activations of AG. Weighing in against such a dissociation are findings of mid-IPS activation in cued recall (Okada et al., 2012). Furthermore, the finding of Guerin and Miller (2011) that activation in several parietal retrieval success areas (precuneus, AG, and IPS) track the strength of face picture memories rather than the decision criterion used in the memory task (in that study, a frequency

judgment) may also be seen as challenging the assignment of an accumulator function to IPS.

One possible modification of the *Accumulator* model in light of the *CoBRA* account might provide a solution to a more general conundrum regarding recognition memory. Recognition requires the prior existence of neural ensembles representing target stimuli. Those ensembles were perceptually activated during acquisition, and achieve representational integrity—binding into a coherent stored representation of a perceptual experience—by Hebbian processes, initially mediated by the medial temporal lobes but later achieving independence through systems consolidation (Dudai, 2004). Recognition is executed by the comparison of such stored representations with a recognition probe. This putative process seems problematic: if the same neural ensemble that was activated during the perceptual acquisition of a memory trace of a given stimulus is also activated by a recognition probe (which is the identical or a very similar stimulus), how are the probe and trace ensembles simultaneously maintained for comparison? This is especially difficult to understand if the comparison occurs over time, as suggested by the *Accumulator* account, since that would seem to involve more complex comparative processes than basic repetition suppression implicated in perceptual priming (Henson and Rugg, 2003). *CoBRA* (Shimamura, 2011) posits that AG is a multimodal perceptual convergence zone supporting consolidated representations (but not representation during initial acquisition); successful recognition recruits the stored representations. Thus, cortical perceptual neural ensembles earlier in the perceptual stream can provide a substrate for a recognition probe, while the AG ensemble might represent the stored memory trace to which it is compared.

A related alternative is that AG might serve as a convergence zone for exogenous recognition probe perceptual inputs which activate more primary perceptual areas and endogenous representations provided by the hippocampus, in order to allow comparisons of perceived and retrieved representations. The degree of overlap between the representations could determine the degree of activation of the AG ensemble. That differential signal could be "read" by another neural ensemble (an accumulator ensemble) that is responsible for a judgment of recognition. That monitoring function might be the provenance of prefrontal areas assigned monitoring functions in mnemonic processes (Moscovitch and Winocur, 2002).

The *CoBRA* account stresses the ability of AG to support multimodal representations, but such a system could support unimodal recognition as needed. A recognition process that can take advantage of the multimodal integrative abilities of AG would provide the most versatile mechanism for ecological recognition. Furthermore, the ability to support integrative multimodal representations could provide the basis for recollective recognition, as well as of cued and free recall of unimodal or multimodal information.

MacKenzie and Donaldson (2009) note that parietal activations are often posited to reflect material-independent retrieval because they have been observed across stimulus types—words, line drawings, object pictures, landscape/object compound stimuli, and sounds. A similar notion is put forward by Donaldson et al. (2010), who go on to suggest that the parietal areas generically accumulate evidence rather than serving as a basis of representations. In contrast, the *CoBRA* account proposes that the lateral parietal regions are activated across material types not because they provide a signal accumulation function, but because of their multimodal integrative capacity.

Some support for the *CoBRA* concept is offered by a case study of a patient with cerebrovascular accident lesions limited to the vicinity of left AG, who was specifically impaired relative to controls in cued recall memory for cross-modal pair associate learning, while exhibiting intact performance on unimodal verbal pair associate learning (Levy, 2010).

The multimodality of representations in AG may explain the findings of Buchsbaum et al. (2011) in a study of recency effects in short-term verbal continuous recognition. They report that an area in middle inferior PPC which exhibited declining activity with increasing presentation-test lag was not active during verbal working memory maintenance, while such maintenance-related activity was found in the more anterior area Sylvian-parietal-temporal (Spt). This finding is taken as indicating that middle inferior parietal activations (themselves dissociated from a yet more posterior region identified with default mode activity) are unlikely to reflect retrieval-related maintenance as assumed by *Output Buffer* account. However, in Buchsbaum et al. (2011), the Spt area was identified using a Sternberg-type working memory task for letters, stressing verbal rehearsal and phonological characteristics, which is unlikely to activate the full range of multimodal stimulus features supported by AG as proposed by the *CoBRA* or *Output Buffer* accounts. Working memory maintenance for more complex stimuli, whether novel or drawn from long-term stores, might recruit AG as well.

In evaluating the *CoBRA* hypothesis, it must be noted that Sestieri et al. (2011), using a movie-based cued recollection paradigm which involves multimodal integration, report that AG was active during retrieval, but that same area was deactivated during a perceptual search task that used very similar materials, as would be expected by the inclusion of AG in the Default Mode Network (see below, "Cognitive Control, Selective Attention, or Default Mode?"). This would indicate that AG is not involved in the basic representation of perceptual information as suggested by *CoBRA*.

An alternative explanation of the activation of AG by retrieval is the *Memory-to-Action* hypothesis (Haramati et al., 2008), which, as mentioned above, is an extension of the *Output Buffer* hypothesis. *Memory-to-Action* is inspired by consideration of two processes in which parietal cortex has been shown to play an important role. The first is in the organization of information for the execution of serial tasks—the capacity which is impaired in ideomotor apraxia, a deficit often linked with left posterior ventral parietal damage (Wheaton and Hallett, 2007). The second point of departure is the complementary roles of parietal and hippocampal regions in navigation. In both animal and human studies, navigation based on allocentric spatial information has been linked to hippocampal substrates, while navigation based on egocentric spatial information has been connected with parietal cortices (Weniger et al., 2009). In fact, Weniger and colleagues (2009) report that in persons with unilateral parietal

cortex lesions, egocentric memory expressed in navigation in a virtual environment is impaired, while allocentric, hippocampal-based navigation memory is spared. Importantly, in rodent studies it has been shown these two entities are not two separate representations, but reflect a transformation of allocentric to egocentric versions of spatial memory which enables the animal to move through the environment (Whitlock et al., 2008). In rodents, the hippocampus is primarily important for the representation of spatial information, but in humans its function seems to have developed to accommodate episodic information in general. The *Memory-to-Action* account speculates that the hippocampal-parietal translation of spatial information in rodents suggests hippocampal-parietal translation of episodic information in humans. Under ecological conditions, the function of retrieved memories is to support action in the environment. Remembering the identity, position, and temporal qualities of features of the world enables us to act efficiently. For this purpose, recognized and recalled items have more intrinsic value (and hence continue to be represented in the buffer) than stimuli that are judged to be novel, since known entities can constrain the degrees of freedom of potential action, while unknown entities provide less guidance for behavior. Similarly, high confidence memory judgments, being subjectively more reliable in guiding behavior, are more likely to lead to post-retrieval buffering than low-confidence judgments; this is in consonance with recent findings (Hayes et al., 2011) that ventral parietal cortex is more strongly activated by high- than by low-confidence endorsements, both for item memory and for item plus source memory. AG might provide a buffer dedicated to translation of memoranda to action-oriented representations. Aside from explaining the AG activations by episodic retrieval, this account addresses the findings that damage to lateral parietal areas do not generally cause mnemonic impairments in the same tasks that lead to the activation of those areas (Schoo et al., 2011). The process of recognition depends on other substrates; after recognition has happened, AG enters the process, so lesions would be expected to affect the subsequent use of retrieved information rather than the retrieval itself. Further research is required into parietal lesion effects on utilization of memory in guidance of subsequent action in order to assess the explanatory utility of this Memory-to-Action model.

This proposal converges with a recent account of the centrality of AG in semantic memory (Binder and Desai, 2011). Based on evidence they cite that AG responds strongly to concrete, high-frequency words and meaningful sentences, Binder and Desai (2011) conclude that the level of AG activation seems to reflect the amount of semantic information that can be successfully retrieved from a given input. Furthermore, they point out that, if considered as a convergence zone, "AG is notably bounded by dorsal attention networks that play a central role in spatial cognition, anterior parietal regions concerned with representation of action and posterior temporal regions supporting movement perception. This suggests that the AG may play a unique role in representation of event concepts" (Binder and Desai, 2011, p. 533). Supporting an action-oriented representation of information drawn from episodic memory may be yet another aspect of representational convergence afforded by such a transmodal association area (Mesulam, 1998).

TIMING: PRE-RETRIEVAL, RETRIEVAL, OR POST-RETRIEVAL?

An additional taxonomy of accounts of parietal mnemonic function can be constructed using a temporal framework. For example, the implication of the *AtoM* account is that the dorsal and ventral parietal foci of retrieval-related activity should be found in two different time windows. The dorsal/superior parietal regions, implicated in focal top-down attention, need to be engaged preceding the actual retrieval, while the ventral foci centered around supramarginal gyrus, activated in bottom-up capture of attention, should come into play after retrieval. The *Accumulator* model and the *CoBRA* account focus on the moment of retrieval itself, for different reasons. The *Output Buffer* and *Memory-to-Action* accounts relate ventral parietal activations to post-retrieval processes, as should the *Expectation* account, since only after retrieval can the mnemonic status of an item be compared with one's expectation.

Evaluating the accounts based on temporal features of experimental data is challenging. Hemodynamic imaging does not have the temporal resolution required for adjudicating these claims, but EEG and magnetoencephalographic (MEG) studies can address the issue. The most recent studies to relate to this issue are those of Seibert and colleagues (2011a,b), in which MEG was recorded during cued recall following pair associate learning. Seibert and colleagues report very early activity—beginning within 100 ms of a retrieval cue and resolving in less than 400 ms—that distinguished correct living/non-living classification of the studied pair member of a presented cue from parallel correct classification of cues themselves. In their second study, taking advantage of the spatial resolution afforded by MEG, Seibert and colleagues (2011a) localize that activity to IPS. They conclude that this finding of very early activation associated with successful retrieval supports the *AtoM* account. It must be noted, though, that the classification responses in the task employed by Seibert and colleagues required retrieval of a limited type of gist information, and do not require the retrieval of the actual identity of the target memorandum. It remains to be demonstrated whether such early responses will characterize fuller episodic retrieval. Furthermore, the temporal differences between the conditions in that study were rather similar in IPL and SPL, contrary to the dorsal/ventral, top-down/bottom-up attention dissociation suggested by the *AtoM* account.

It is therefore instructive to examine earlier electrophysiological studies of episodic retrieval, which served as the original basis of claims for the existence of parietal mnemonic processes. The discussion of event-related potentials recorded over parietal scalp elicited in conjunction with successful recognition generally focuses on the 500–900 ms time range (Allan and Rugg, 1997; Friedman and Johnson, 2000; Rugg and Curran, 2007). The parietal components reach their strongest voltages later than those recorded over frontal scalp; they are also posited to reflect recollective richness in contrast to simple familiarity associated with the frontal foci (Rugg and Curran, 2007), although the interpretation of the frontal aspect is controversial (Voss and Federmeier, 2011). The question is whether that 500–900 ms time window is early or late, in the context of mnemonic processes. For example: in a simple word recognition task, in which the mean response time is 700 ms, the old/new ERP difference peaks at 600 ms on

average, but extends from 400–900 ms (Johnson et al., 1998); can that ERP be conclusively identified as reflecting pre-retrieval, retrieval or post-retrieval processes? Furthermore, several studies have documented a late posterior negativity which extends several hundred ms after responses are made (e.g., Johansson and Mecklinger, 2003; Friedman et al., 2005; Herron, 2007; Mecklinger et al., 2007). This very robust activity, with old/new voltage differences sometimes several times stronger than differences in the window of earlier old/new parietal differences, is observed in tasks in which response conflict is potentially strong, or when additional information about the encoding episode (source memory) is to be retrieved. It may be argued that specifically those experimental conditions may serve as good models of ecological remembering, in which information may subjected to further analysis after its retrieval, in order to apply it to needs of the situation in which the rememberer is functioning. This contrasts with the standard serial recognition judgment paradigm in which activity is tracked in the laboratory, in which the task characteristics encourage the participant to cease processing the retrieved stimulus immediately after the recognition judgment in order to be ready for the next trial.

Thus, EEG and MEG studies have documented several time windows of parietal activation, which when taken together are compatible with the temporal characteristics of all of the extant accounts of parietal mnemonic activations. This suggests that parietal activations may represent a number of cognitive functions occurring during different epochs of retrieval processes, modulated by task demands. The implication of this distribution would be that several of the parietal mnemonic accounts might be valuable for understanding the activations in question, and they might therefore tile the time continuum rather than providing conflicting explanatory alternatives.

Another approach to determining the assignment of activations to slots in the sequence of retrieval stages is offered by the studies of Herron et al. (2004) and Vilberg and Rugg (2009). They employ a manipulation of the relative probability of old and new items in blocks of the test battery, for item recognition in the former study and for source judgments in the follow-up study. The assumption of that manipulation is that "neural activity can only vary according to the relative probability of old and new items after the items have been identified as such" (Vilberg and Rugg, 2009), and modulation by probability indexes post-retrieval processes, but not retrieval itself. Vilberg and Rugg (2009) report that two superior parietal regions, one anterior and one posterior to mid-IPS, showed such probability-sensitive retrieval success effects. In contrast, source-retrieval-related activations in ventral regions in the vicinity of AG and mid-IPS activation irrespective of source accuracy were insensitive to old/new probability differences. This represents a "process-dissociation" approach to unraveling the temporal structure of parietal mnemonic activations.

An extension of the temporal taxonomy is the question of the relationship between parietal retrieval effects and parietal encoding effects that have been investigated in other studies. Notably, it has been reported that 85% of the positive subsequent memory effects in the lateral PPC occurred in superior parietal regions (in the IPS or BA 7 dorsal to it), while activation in more ventral parietal areas during encoding predicts subsequent forgetting (reviewed by Uncapher and Wagner, 2009; Kim, 2011). This distribution of effects has been explained in terms of attention: top-down attention during encoding, supported by superior parietal substrates, yields more effective encoding and better memory, while the capture of attention by non-target stimuli in the environment, or DMN-related mind wandering, leads to less effective encoding and so to poorer subsequent memory (Uncapher and Wagner, 2009; Kim, 2011). Such findings and explanations are differentially challenging for the various accounts of retrieval effects. In the accounts that assign parietal activations to attentional or signal accumulator processes, parietal retrieval effects may be completely orthogonal to encoding effects. However, the contrast between the existence of retrieval success and the lack of subsequent memory effects in AG is a challenge to the *CoBRA* account, and to the *Output Buffer* hypothesis as well. If parietal mnemonic activations at retrieval reflect memory contents rather than memory processes, we might expect greater encoding-retrieval overlap than is reported. This would certainly be the case according to the view that an act of remembering, especially episodic remembering, consists of the coordinated reactivation of sensory/perceptual regions that were activated at the time of encoding (e.g., Squire, 1987; Wheeler et al., 2000). Studies using fMRI have provided evidence supporting this reactivation/reinstatement hypothesis (e.g., Johnson and Rugg, 2007; Kim et al., 2010; and other studies reviewed by Danker and Anderson, 2010). If AG plays a content role, as suggested by *CoBRA*, we should expect to find encoding-retrieval overlap. However, this has not been reported; indeed, in one study, higher-levels of AG activation during the presentation of task-irrelevant face pictures were correlated with subsequent failure to recognize those faces (Minamoto et al., 2012). That heightened activation in ventral parietal regions during encoding leads to subsequently poorer memory is in accordance with the *AtoM* account: because items to be encoded are ostensibly in the focus of attention, during encoding there is typically no need for attention reorienting. Thus, VPC activity at encoding may reflect bottom-up attention to task-irrelevant stimuli or thoughts, and hence predict encoding failure (Daselaar et al., 2009).

An additional temporal frame issue poses another challenge to one feature of the *CoBRA* account. According to *CoBRA* (Shimamura, 2011), AG is especially important for supporting consolidated episodic representations, which at an earlier stage in their lifespan are more dependent on the hippocampus. Such systems consolidation (Dudai, 2004) of memory from initial medial temporal lobe representations to posterior cortical substrates has indeed been posited by many memory theories. However, the time frame of systems consolidation in humans may range from days to decades—while AG activations during retrieval have been reported when retrieval follows encoding by less than an hour. This seems to be problematic for that aspect of the *CoBRA* hypothesis.

VERIDICAL OR ASSERTED MEMORY?

The various accounts of parietal mnemonic activations may also be assessed on the basis of how well they fit in with the reports that lateral parietal activity is correlated with the subjective impression

that an item is old, such that it is found in false alarms more than in correct rejections (Wheeler and Buckner, 2003; Kahn et al., 2004; Shannon and Buckner, 2004; Wagner et al., 2005). This is most problematic for the *CoBRA* account, since that proposal relates the activations to the existence of representations in cortex, which theoretically should not exist for foil probes. Subjective memory activations require the *AtoM* account to incorporate the capture of attention not by mnemonic representations themselves (since there are no such representation in the case of false alarms) but by the cues that are used to probe it. It also requires the *Accumulator* hypothesis to accept that the signal cannot be the raw comparison of probe to representation, but rather the output of an earlier process that has already made that comparison, and requires the *Output Buffer* hypothesis to allow the storage in the buffer of a probe-related representation rather than retrieved information alone. The activation by subjective judgment is least problematic for the *Memory-to-Action* hypothesis, as it posits that a post-retrieval-decision trace is what is held in a buffer for further processing, whether it is veridically old or not. It is notable in this regard that neuropsychological findings have led some researchers to suggest that parietal cortex does not directly participate in retrieval, and instead reflects the subjective experience of recollection (Ally et al., 2008).

In a related vein, O'Connor and colleagues (2010), using a Posner cueing paradigm adapted for a recognition memory, show that ventral parietal activation (in both the AG and supramarginal gyrus) is more sensitive to expectation of whether an item would be old or new than to whether it was actually old or new. Such expectation judgments are theoretically orthogonal to the veracity of the mnemonic judgment. However, the trial-by-trial cueing in that study changes the cognitive nature of the task, and focuses the participant on constant evaluation of the cue-stimulus relationship, and therefore it is uncertain whether that pattern of findings readily generalizes to ordinary retrieval task processes.

QUANTITY, QUALITY, OR STRENGTH?

It has been observed that "AG retrieval-related activity has been reported to covary with the amount of information recollected" (Hayama et al., 2012), supporting a content approach to understanding such activations. However, determining whether particular experimental conditions yield differences in ecphoric quantity or quality is not trivial. For example, Guerin and Miller (2011) describes the difference between memory for stimuli presented 1–2 times and stimuli presented 5–6 times as being "the amount of information recollected," and suggests interpreting recognition-related activations which they found in AG accordingly. But does stimulus repetition necessarily lead to quantitative information differences? Even if repetition increases the *likelihood* of recognition (and therefore of measures of performance such as percent correct scores), it may not increase the *amount* of information available for each individual recognized stimulus. Of course, interpretation of repetition effects is a function of what one means by the "amount of information." If one is given the task of remembering object pictures, e.g., successful encoding of the name of the object or basic aspects of its appearance would enable recognition in contrast to foils that are other objects, but not necessarily in contrast to foils that are minimally modified versions of the original object. The additional details required for the latter task might best capture the idea of "amount of information" about a recognition target, and their acquisition might be a function of repetition. This does not seem to have been investigated.

Suzuki and colleagues (2011) employed encoding repetitions, but understand them as affecting memory strength rather than quantity of information. They conducted fMRI while participants made responses indexing the initial, second, third or fourth appearance of object pictures. They report that while mid-IPS activation increased linearly with the degree of repetition, no such effect was found in more ventral parietal areas. They interpret that absence of activation as possible evidence that the repeatedly presented items elicited little or no recollection. However, the authors do not report whether retrieval success effects were not found at all in VPC, or whether they were found, but not repetition-graded.

Another approach to operationalizing memory strength is based on ratings of confidence in mnemonic judgments. Hayes and colleagues (2011) contrasted differences in confidence during tasks requiring item or source retrieval, and report that parietal mnemonic activity tracked confidence ratings, with dorsal areas showing low-confidence activity and anterior ventral areas in the vicinity of BA 40 showing high-confidence activity in both tasks. This finding is offered in support of the *AtoM* account.

Turning to qualitative distinctions, source memory retrieval success is often offered as evidence for qualitative differences in memory processes (e.g., within a dual-process framework; Yonelinas, 2002). However, source memory judgments employed in parietal mnemonic studies are generally binary (e.g., which task—pleasantness or concreteness judgment—was used for encoding this stimulus? Did this stimulus previously appear on the right or left of the screen? Was it presented in red or in green?). Few studies provide multiple opportunities to retrieve information about the encoding episode—which could provide a quantitative rather than qualitative characterization of memory for retrieval incident.

Furthermore, and in connection with the above-mentioned proposal that AG might serve as a convergence zone for exogenous recognition probe perceptual inputs in order to allow comparisons of perceived and retrieved representations, is a key and often overlooked point regarding experimental studies of recognition. Although they are sometimes purported as being able to dissociate familiarity from recollection (Yonelinas, 2002), recognition tests are nevertheless invariably tests of *contextual* recognition, which is problematic for the assessment of familiarity. Certainly in recognition tests employing verbal materials, and even for recognition tests using novel visual or auditory stimuli, participants are seldom if ever asked if a probe stimulus is at all familiar—whether they have ever experienced it at any point in the past. Invariably, the test question always is: Did you experience this stimulus *in the encoding episode*? Thus, the standard recognition memory experiment does not identify processes supporting simple familiarity, but rather processes enabling the linkage of a stimulus with a particular spatio-temporal context. Context is a multisensory entity; accordingly, if AG provides a multimodal convergence zone, it has added value for recognition not in representation of

the probe or target stimulus, but vis-à-vis the context in which it was experienced. Therefore, remember-know response types may index differences in degree of memory strength rather than in categorical differences.

LATERALIZED OR BILATERAL?

Two domains have been noted in which lateralization of parietal mnemonic activations require consideration: material type specificity (e.g., verbal vs. visual stimuli) and retrieval-type specificity (recognition vs. cued recall).

Left-lateralized PPC activity has been observed for non-verbal information (faces) and non-visual information (Guerin and Miller, 2009), words, pictures, and sounds (Shannon and Buckner, 2004). It should be noted that the effect lateralization may be relative, as a function of the activation threshold selected for report. For example, in Shannon and Buckner (2004), parallel (albeit weaker) activations are reported in the right parietal areas activations for the same stimuli that activated the left hemisphere. For non-Western, non-verbal music clips assumed to be encoded and represented primarily by higher-order auditory regions in the right-hemisphere successful retrieval effects were observed only in the right PPC (Klostermann et al., 2009). It is possible that the dominance of left-lateralized effects reflects the use of left hemisphere verbal or semantic retrieval processes (Shimamura, 2011), perhaps even for materials such as faces, for which right-hemisphere perceptual representations are dominant, but for which descriptive heuristics may be employed as part of a recognition strategy.

Left lateralization of ventral parietal activations is problematic for the *AtoM* account, as much recent evidence indicates that non-spatial attentional abilities such as detection of behaviorally relevant and novel stimuli and reorienting to stimuli in either visual field that are presented outside the focus of attention (stimulus-driven reorienting) recruit a right lateralized ventral attention network (Corbetta and Shulman, 2011). It would therefore be expected that reorienting of attention to retrieved information on the basis of its salience (Cabeza et al., 2008, 2011) would lead to stronger right-hemisphere activations, irrespective of material type. Content accounts of parietal mnemonic activations are more compatible with material-specific or semantically driven lateralization.

In contrast to the left-lateralization of parietal recognition-related activations, event-related potential, and hemodynamic imaging studies of cued recall sometimes report more bilaterally distributed parietal activations (e.g., EEG: Allan et al., 1996; Allan and Rugg, 1997, but not Donaldson and Rugg, 1999; fMRI: Schott et al., 2005; Hayama et al., 2012 but not de Zubicaray et al., 2007), and we have found this to be the case for EEG recorded in conjunction with cued recall following audio-visual pair associate learning as well (Levy, unpublished data). This might account for the finding by Davidson et al. (2008) that in patients with PPC lesions (four left- and one right-hemisphere lesions), impairment was observed on an old/new recognition test and patients offered fewer "remember" and more "know" responses than did controls. In contrast, the patients were not significantly impaired on the cued recall or source memory tests. Since cued recall has been reported to have a more bilateral activation distribution, compensation by the intact hemisphere might have been more effective specifically for that task. As noted by Hayama et al. (2012), this distribution might also explain the lesion data of Simons et al. (2010).

COGNITIVE CONTROL, SELECTIVE ATTENTION, OR DEFAULT MODE?

Default mode

An important recent concept in cognitive neuroscience is the functional parcellation of the brain into networks supporting externally oriented active perception and goal-directed cognition and networks supporting internally oriented mentation, with the latter often referred to as the (DMN; Raichle et al., 2001). Noting the overlap between membership of the parietal aspects of the "retrieval success network"—AG, posterior cingulate cortex, and the precuneus—and their membership in DMN, Kim (2012) suggests that the optimal approach to understanding retrieval-related activations in AG is in terms of its belonging to DMN. Similarly, Kim (2012) suggests that the dorsal parietal mnemonic activations should be understood in terms of those areas being part of the cognitive control network, along with a range of prefrontal regions.

However, some recent findings seem to vitiate the explanatory power of the default mode account for AG-focused old-new effects. In a study by Sestieri et al. (2011), participants performed cued recollection of details of previously movie scenes, arguably a strong model of ecological recollection. They report dissociation within the DMN areas between AG which was implicated in such retrieval processes, and mPFC, which was not so involved. Similarly, Suzuki et al. (2011) report dissociation in repetition effects between the precuneus, which like IPS showed graded increase with repetition, and hippocampus and retrosplenial/posterior cingulate cortex, which showed a graded decrease of activation. Reas et al. (2011) report that in the course of attempted recall of strongly and (especially of) poorly remembered word-pair associates, participants exhibited deactivation in left inferior parietal lobe in the vicinity of AG (along with anterior hippocampus and other aspects of DMN). This is very much the opposite of what might be expected on the basis of prior studies that report that the degree of AG activation increases with greater recollective strength, from a form of retrieval that would seem to require the greatest degree of recollection. Furthermore, in an experiment that tracked the effects of word study-test lag on retrieval-related activations, Buchsbaum et al. (2011) found that both a medio-lateral inferior parietal area that showed decreasing activation with longer lag, and an anterior temporal-parietal region abutting the Sylvian fissure implicated in basic verbal working memory rehearsal, were functionally and anatomically dissociable from a third, more posteriorly situated, parietal area identified with DMN. Such divergent dissociations seem to indicate that explanations of lateral parietal activations simply in terms of general DMN processes may not be an effective approach.

Cognitive control

Consideration of the second putative network implicated in parietal mnemonic activations, which Kim (2012) labels the cognitive

control network, intuitively brings to mind the *AtoM* hypothesis (Cabeza et al., 2008, 2011; Ciaramelli et al., 2008, 2010). That account posits that dorsal parietal activations reflect allocation of attention to memory search. Understandably, to the extent that superior parietal lobes are a substrate of top-down attention processes (Corbetta and Shulman, 2002, 2011), it is to be expected that just as in any cognitive process, attending to the task will bring greater chances of its successful execution. This proposal is supported by findings that more challenging instances of successful recognition—e.g., recognition judgments which are identified as reflecting familiarity rather than recollection, or those with low-confidence—are more likely to be associated with superior parietal activations than recollective, high-confidence, ostensibly less effortful recognition. Additionally, DPC activity has been found to decrease across repeated retrieval attempts (Kuhl et al., 2007).

Recently, Ciaramelli et al. (2010) have noted that dorsal parietal activations—specifically in the IPS—are associated with trials in which probes are preceded by cues that could initiate retrieval before probe presentation. However, in that study, the cues were all studied words in themselves, so the evidence accruing from it that activation reflected orienting rather than automatic retrieval is equivocal.

Counter to the *AtoM* claims that dorsal parietal activations are purely attentional is the integrative analysis reported by Hutchinson et al. (2009), indicating that foci of dorsal parietal activation in studies of recognition do not completely overlap the foci of activations from studies of visual attention and working memory. Hutchinson and colleagues report that top-down attention foci are mostly to be found in the medial bank and posterior portion of IPS, and in SPL, while retrieval success activations lie lateral to most attentional foci. However, Hutchinson and colleagues acknowledge that divergence may represent the specific types of visual-spatial attentional foci that they compiled for comparison, whereas recognition memory tasks might recruit slightly different attentional processes. A recent specific examination of the dorsal parietal activations by Sestieri and colleagues (2010), in which retrieving remembered details of a viewed video clip was contrasted within subjects with perceptual search of the same kinds of details, yielded IPS activations that not only did not overlap, but actually suggested competition between attentional and mnemonic processes.

There are, of course, other cognitive processes other than purely attentional ones with which dorsal parietal mnemonic activations might be linked. Kim (2012) notes that across studies, components of the cognitive control network are activated more strongly by instances of source retrieval than of item retrieval. Among the possible reasons for that difference is the fact source memory judgments are generally made between two alternatives. A generate and test approach can be used in order to weigh the relative similarity of each of the possible representations compared with a stored representation. Thus, source judgments may use working memory, in which superior parietal cortex is strongly implicated (Wager and Smith, 2003) to represent the alternatives and judge between them, while in item recognition the entire probe is perceptually available until judgment.

Another cognitive control distinction, suggested by Kim (2012), is that iterative searches and verification of retrieved information may engage more consistently during a hit than during a correct rejection of an unstudied probe. However, it seems that at least iterative searches must be more part of the correct rejection process than of the recognition hit process, just as in visual search tasks reports of target presence must be faster on the average than reports of absence. An alternative is provided by the *Expectation* account, based on the study of Herron et al. (2004), who showed that areas implicated in cognitive control, but not default mode areas, retrieval success effects decreased or even reversed when old/new stimulus ratios increased from 25 to 75% of the test probes. Sensitivity to probability reflects an executive function/cognitive control account which is applicable not just to memory judgments, but to perceptual decision-making in general, as indicated by the study of Ploran et al. (2007). The involvement of such processes in mnemonic judgments and their independence from purely selective attention processes may be related to the report of Vincent and colleagues (2008) of three networks dissociated by resting-state connectivity, which they identify as representing dorsal attention, fronto-parietal control, and hippocampal-cortical memory systems. These systems occupy a progressively superior-rostral to inferior-dorsal swath along lateral parietal cortex. The fronto-parietal control aspect of these networks seems to overlay the convergence maps of retrieval success and recollection effects provided by Hutchinson and colleagues (2009). It therefore seems appropriate to conduct additional parietal mnemonic studies tracking the impact of the range of factors implicated in strategic "working-with-memory" processes on activations in the midrange parietal areas directly inferior to mid-IPS.

Selective attention

The *AtoM* account's attempt to interpret ventral parietal activations in terms of attentional processes—as representing "reorienting of attention to internal representations"—seems somewhat more problematic than the attentional account of dorsal parietal activations. In the integrative analysis of Hutchinson and colleagues (2009), the divergence between memory- and attention-related activations in ventral PPC is quite strong. More recent studies with a higher spatial resolution (e.g., Sestieri et al., 2011) confirm that lack of concordance. The real difficulty with the *AtoM* account, though, is conceptual. What might it mean "to orient attention toward internal representations" in the context of a probe-driven recognition task? Ciaramelli et al. (2010) frame the *AtoM* claim by focusing on non-cued and invalidly cued recognition trials (i.e., recombined pairs), for which activation was found in the AG. However, that operationalization may not capture orienting, but rather the need for recollective processes that are recruited for recognition of a probe when it is not supported by its study context (Tibon et al., 2012).

In a recent study, Cabeza and colleagues (2011), attempted to address the attention-mnemonic foci overlap discrepancies, and address the conceptual issue of nature of orienting in the context of retrieval. Participants learned progressive word-pair chains constructed on the basis of serial semantic associations. They then were presented with the initial word of such a chain and asked to recall the second member of the third linked pair

in that chain. This retrieval condition was contrasted with a task of similar duration, in which participants monitored a stream of letters and noted the appearance of a vowel. The authors propose that the initial stimulus in each case requires orienting to the task case, while the appearance of the vowel target or the retrieval of the target word were both incidents of detection. Overlapping (but not identical) activations were found in dorsal parietal regions for the orienting aspects of both tasks, while overlapping activations in ventral parietal regions were associated with the detection phases. Furthermore, in ROI analyses, the parietal areas showing greater mnemonic detection activation were functionally connected with MTL, while those showing greater perceptual detection activation were functionally connected with visual areas. Cabeza and colleagues (2011) argue that these findings suggest that ventral parietal activations associated with target detection are attentional in nature. However, in this paradigm, detection is stressed at the expense of retrieval. Since the target word was the third retrieval in a chain, it was characterized not only by retrieval processes (in which functional connectivity with MTL is appropriate) but by the fact that a target was identified. Significantly, the authors note that the ventral parietal activations did not differentiate between successful and unsuccessful retrieval when examined in a whole-brain analysis. This contrasts with the cases in which studied stimuli yield ventral parietal activations even when they are not the cases to be endorsed (Shannon and Buckner, 2004; Donaldson et al., 2010). Therefore, that study does not necessarily aid characterization of the specifically mnemonic processes in which ventral parietal areas are implicated. Accordingly, the intriguing concept of orienting to internal representation seems to require further explication.

CONCLUSION

As we have seen, despite the wealth of studies that have been conducted about lateral parietal involvement in long-term episodic memory, uncertainties still abound. Some of the accounts mentioned above maintain that there is nothing specifically mnemonic about parietal activations, but rather that they reflect general purpose attentional or control processes that can support a wide range of cognitive abilities. In other accounts, parietal activations during episodic retrieval are held to reflect aspects of perceptual representation. The interpretive dichotomies of the preceding sections are offered as a heuristic for consideration of the wealth of evidence that has become available regarding this issue. Considered synoptically, they suggest that future research should be oriented toward revealing the mosaic of dimensions characterizing parietal mnemonic processes: delineating subareas (including laterality) and time windows; expanding the range of material types examined; and most importantly—using more ecological assays of memory that can reveal the complex cognitive interactions that may characterize the intersection of perceptual, attentional, mnemonic, and action processes that represent parietal contributions to remembering.

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Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control

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Although much less is known about human parietal cortex than that of homologous monkey cortex, recent studies, employing neuroimaging, and neuropsychological methods, have begun to elucidate increasingly fine-grained functional and structural distinctions. This review is focused on recent neuroimaging and neuropsychological studies elucidating the cognitive roles of dorsal and ventral regions of parietal cortex in top-down and bottom-up attentional orienting, and on the interaction between the two attentional allocation mechanisms. Evidence is reviewed arguing that regions along the dorsal areas of the parietal cortex, including the superior parietal lobule (SPL) are involved in top-down attentional orienting, while ventral regions including the temporo-parietal junction (TPJ) are involved in bottom-up attentional orienting.

Keywords: attention, bottom-up attention, capture, inferior parietal lobule (IPL), parietal cortex, superior parietal lobule (SPL), temporo-parietal junction (TPJ), top-down attention

INTRODUCTION

Successful interaction with our sensory environment requires an intricate balance of two attentional selection mechanisms—that of top-down and bottom-up. Heading over to the produce aisle of your local supermarket with the goal of picking up few needed ingredients for the mango salad, engages deployment of voluntary goal-directed, or top-down, attentional system such that you actively search for all the required ingredients among the multitude of produce choices. However, should you hear a ringer of a cell phone, it will most likely capture your attention and interrupt your search. Such interruption occurs in a bottom-up, or stimulus-driven, fashion whereby a mere salience of the stimulus, the fact that the ring is different from other sounds in your environment, deems it worthy of selection. The described scenario underscores the importance of goal-directed and stimulus-driven selection for behavior, and points to a fine balance that has to exist between the two attentional systems to prevent "tunnel vision" on the one hand and complete inability to focus on the other.

TOP-DOWN AND BOTTOM-UP SELECTION: BEHAVIOR

Several decades of behavioral research have been dedicated to demonstrating that the distribution of attention can be controlled by intentions of the observer as well as by the salience of the physical stimulus. Much of behavioral evidence for top-down and bottom-up attentional allocation has been reviewed extensively elsewhere (Johnston and Dark, 1986; Egeth and Yantis, 1997). To summarize, studies demonstrating effects of top-down attentional control show that attention can be successfully allocated to spatial locations, features, objects, etc., following presence of exogenous or endogenous cues (Eriksen and Hoffman, 1972; Posner, 1980; Posner et al., 1980), or expectations either set by prior knowledge or by contingencies of the stimulus (Shaw, 1978; Moore and Egeth, 1998; Geng and Behrmann, 2002, 2005; Shomstein and Yantis, 2004a; Drummond and Shomstein, 2010). Evidence supporting bottom-up attentional allocation has relied on various attentional capture paradigms, in which participants are engaged in a top-down search and their attention is diverted to the task-irrelevant stimuli, demonstrating that attention is captured by feature singletons (unique item; Yantis and Jonides, 1990; Theeuwes, 1991; Folk et al., 2002) and abrupt onsets (Yantis and Jonides, 1984; Theeuwes, 1991; Koshino et al., 1992; Juola et al., 1995).

Whereas most early studies concentrated on demonstrating evidence for top-down and bottom-up attentional selection, most recent studies shifted their focus to examining how the two attentional selection systems interact. This line of investigation is fueled by observations that in order to effectively select task-relevant information (e.g., ingredients for the salad) one must actively inhibit the task-irrelevant information that would otherwise divert attention away from the task at hand. The flip side of this logic, is that the less one is focused on task-related information the more capture will ensue. It has been shown experimentally that the attentional state of the observer predicts what type of information, and to what extent, will ultimately capture attention (Folk et al., 1992, 2002; Bacon and Egeth, 1994; Gibson and Kelsey, 1998). For example, Folk et al. (2002) showed that when searching for a red letter, an observer will be more readily captured by an irrelevant stimulus in the periphery if that stimulus is red, or matches the target template in some way. Since the observer's top-down control settings are set to search for a red feature, any stimulus that is red is likely to capture attention and potentially interfere with top-down control. Thus, with a capture task, attentional search strategies can be distinguished from one another by varying the similarity levels between the stimulus properties of the target and distractors. The more similar the target is to the distractor, the more difficult it is for the observer to avoid capture.

THE ROLE OF THE PARIETAL LOBE IN TOP-DOWN AND BOTTOM-UP SELECTION: NEUROIMAGING

Various neuroimaging techniques provided strong evidence for the involvement of parietal cortex in top-down and bottom-up orienting, with the evidence reviewed extensively elsewhere (Corbetta and Shulman, 2002, 2011; Behrmann et al., 2004). It has been demonstrated that areas most commonly activated following top-down cues to attend to particular locations, features, or objects are located along the dorsal parts of the parietal cortex. Such areas include inferior parietal lobule (IPL), dorsomedial regions referred to as superior parietal lobule (SPL), as well as more medial regions along the precuneus gyrus (Yantis et al., 2002; Giesbrecht et al., 2003; Liu et al., 2003; Yantis and Serences, 2003; **Figure 1**). Several top-down tasks have been shows to successfully engage dorsal regions of the parietal cortex, namely those involving spatial (Kastner et al., 1999; Corbetta et al., 2000; Hopfinger et al., 2000; Shomstein and Behrmann, 2006; Chiu and Yantis, 2009; Greenberg et al., 2010) as well as non-spatial shifts of attention (Giesbrecht et al., 2003; Yantis and Serences, 2003; Shomstein and Yantis, 2004b, 2006; Tamber-Rosenau et al., 2011).

In a typical task aimed to engage the top-down attentional allocation, individuals are shown two rapid serial visual presentation (RSVP) streams positioned peripherally and are initially instructed to monitor one stream for a cue (e.g., a digit among the stream of letters). The identity of the cue indicates whether the subject must maintain attention on the current stream or shift attention to the other stream (Yantis et al., 2002; Yantis and Serences, 2003). Two major findings are observed in such paradigms. The first has to do with increased activation within the sensory regions representing the at-the-moment attended location (e.g., increased activity within the left primary visual regions when the right RSVP stream is attended). This finding provides firm evidence that participants are attending to a specific location and that attention modulates the strength of the sensory response (see **Figure 1**; Moran and Desimone, 1985; O'Craven et al., 1997). The second finding has to do with the observation that dorsal regions of the parietal lobe are selectively activated by shifts of top-down attention. It is observed that the SPL/IPL timecourse of activity is transient in nature suggesting that this area of the parietal cortex is the source of a brief attentional control signal to shift attentive states in a top-down manner (Yantis et al., 2002).

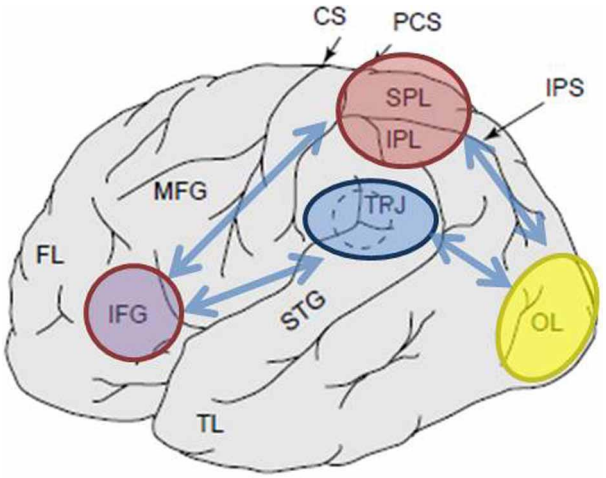

FIGURE 1 | Schematic depiction of relevant anatomical landmarks projected onto the lateral surface of the human brain. Superior parietal lobule (SPL) and inferior parietal lobule (IPL) are regions within the dorsal part of the parietal cortex subserving top-down attentional orienting. Temporo-parietal junction (TPJ) is a region within the ventral parietal cortex subserving bottom-up attentional orienting. Both, SPL and TPJ, are thought to elicit control signals responsible for subsequent attentional modulations observed over sensory regions, in this case modulating (labeled with dark blue arrows) visually evoked activity in the occipital lobe (OL). Additionally, areas along the inferior frontal gyrus (IFG) and inferior frontal junction (IFJ) are thought to serve as convergence areas for stimulus-driven and top-down attentional control (marked by light blue bi-directional arrows).

Several fMRI studies have documented that bottom-up attentional capture, mediated by stimulus salience and/or relevance, is subserved by the temporo-parietal junction (TPJ; **Figure 1**). For example, when subjects attend to and monitor a change in either a visual or auditory stimulus, presented simultaneously, activation of the TPJ regions of the parietal lobe is enhanced. In addition to the apparent sensitivity to relevant stimuli, TPJ is also activated in response to potentially novel (unexpected or infrequent) events when an organism is engaged in a neutral behavioral context or when engaged in a task (Marois et al., 2000; Downar et al., 2002; Serences et al., 2005; Corbetta et al., 2008; Asplund et al., 2010; Diquattro and Geng, 2011; Geng and Mangun, 2011). This activation occurs independent of the modality (auditory, tactile, and visual) in which the input is delivered, reflecting multisensory nature of TPJ (but see Downar et al., 2001).

In a typical task examining the neural mechanism of bottom-up attentional capture, participants are presented with an RSVP stream of items in the center of the display and are asked to identify a pre-defined target (e.g., identify red letter presented within an RSVP stream of white non-targets). Some proportion of trials contains a task-irrelevant salient distractor presented at various time intervals prior to the onset of the target, while other trials contain only the salient distractor (i.e., without the target). "Target-distractor" trials are used in order to assay the extent of capture, showing that the task-irrelevant distractor is in fact salient thereby yielding a decrease in target accuracy. The "distractor-in-isolation" trials are used for further analyses since such trials allow for the examination of activity elicited to the salient distractor without contamination from the target-related processes. Several important findings emerge from such paradigms. First, when distractors are spatially separated from the target location, capture distractors are accompanied by increased cortical activity in corresponding regions of the sensory cortex (e.g., retinotopically organized visual cortex; see **Figure 1**). Such results provide strong evidence that during capture, spatial attention is in fact captured to the spatial location occupied by the distractor (Serences et al., 2005). Second, ventral regions of the parietal cortex, mainly within the TPJ are selectively activated by bottom-up, involuntary, shifts of attention. Just as activity within the SPL for the top-down orienting, the timecourse of activity observed over TPJ is transient in nature suggesting that this region is the source of a

brief attentional control signal to shift attention in a bottom-up manner.

It should be noted that while this review is focused on addressing cognitive functions of the posterior parietal cortex, other regions, notably those within the frontal cortex are also recruited for top-down and bottom-up attentional allocation. Such regions include the ventral frontal cortex (VFC), the frontal eye fields (FEF), inferior frontal junction (IFJ), and inferior frontal gyrus (IFG; Corbetta and Shulman, 2002, 2011; Serences et al., 2005; Asplund et al., 2010; Diquattro and Geng, 2011).

THE ROLE OF THE PARIETAL LOBE IN TOP-DOWN AND BOTTOM-UP SELECTION: NEUROPSYCHOLOGY

Historically researchers relied critically on neuropsychological studies of patients with hemispatial neglect (a disorder of spatial allocation of attention to the left hemi-space) to gain insight into cognitive functions associated with the parietal lobe. In the classical neuropsychological literature, parietal cortex, as an entirety, was generally considered the primary lesion site for hemispatial neglect. This view, elaborated in detail by early researchers (Critchley, 1953; McFire and Zangwill, 1960; Piercy, 1964) clearly recognized the association between the parietal lesion and the ensuing neglect. This perspective was largely held through the 1980s when Posner and colleagues (1984) used the covert visuospatial cueing paradigm to show that damage to the parietal lobe produces a deficit in the "disengage" operation (retracting attention from one location and shifting it to another) when the target is contralateral to the lesion. However, despite this major advance in understanding the neural basis of attention and specifically the "disengage" role of parietal cortex, their findings assume a single cortical site (parietal cortex) and a single functional capability ("disengage"). In contrast with this more monolithic approach to the brain (parietal cortex) and behavior (attentional disengagement), recent behavioral and neuroimaging work (reviewed above and elsewhere) suggests that both the cortical region and the associated attentional behavior may be subdivided into qualitatively different profiles.

Given segregation of the cortical networks into top-down and bottom-up processes, an obvious prediction is that damage to superior portions of the parietal lobule (subsuming SPL) should yield a deficit in goal-directed attentional orienting, whereas damage to the inferior portions of the parietal lobule (subsuming TPJ) would result in a deficit associated with stimulus-driven attention capture. To the extent that these brain-behavior correspondences have been explored in the neuropsychological literature, this prediction is not obviously upheld. For example, clinical symptoms of hemispatial neglect are strongly associated with damage to the inferior portions of the parietal lobe, which includes TPJ, rather than to superior portions like SPL (Friedrich et al., 1998; Shomstein et al., 2010; Corbetta and Shulman, 2011). This is somewhat at odds with the neuroimaging literature, which suggests that the role of TPJ is in the capture of attention, rather than in the voluntary orienting of attention, the domain in which neglect patients seem to have the most difficulty. To complicate matters further, it has been noted that lesions that involve SPL exclusively, only rarely produce clinical evidence of neglect (Vallar and Perani, 1986). Another recent study with patients with lesions centered primarily over TPJ and STG but preserved SPL, Corbetta et al. (2005) showed that spatial neglect, as well as its recovery, was associated with restoration of activity in *both* the ventral temporo-parietal and dorsal parietal regions (see Corbetta and Shulman, 2011 for a review). While interesting and exciting in its conclusions, this last study does not differentiate the relative contribution of dorsal and ventral pathways to different types of attention, since patients were only tested on a variant of the Posner covert spatial attention cuing task, task that is thought to engage both top-down and bottom-up attentional orienting.

To distinguish between goal-driven attentional control and salient attentional capture and to examine their mapping onto the SPL and TPJ, respectively, recent study adopted two behavioral paradigms, each targeting one of these forms of attention (Shomstein et al., 2010). To examine the integrity of top-down attentional orienting in the patients, a top-down task was used requiring participants to shift spatial attention between the spatially separated RSVP streams (a task that has been successfully used to demonstrate SPL activation in fMRI studies (Yantis et al., 2002)). Similarly, in order to examine the bottom-up attentional orienting abilities of the patients, a variant of Folk et al. (2002) contingent capture paradigm was employed in which participants detected targets that appeared at fixation while task-irrelevant color singletons were flashed in the periphery. The extent to which task-irrelevant distractors interfere with the central detection task was then used as a measure of bottom-up attentional capture (Bacon and Egeth, 1994; Folk et al., 2002).

The predictions were as follows: patients with lesions to superior portions of the parietal lobe (affecting SPL) should be impaired in the top-down attentional orienting task (with preserved performance on the capture task) while patients with lesions to the inferior portions of the parietal lobe (affecting TPJ) should be impaired on the capture task (with spared performance on the top-down task). A double dissociation of this form not only attests to the independent components of attention but also suggests that such attentional components are mediated by independent neural mechanisms. Eight patients with visuo-spatial neglect were recruited for the study and completed two tasks, tapping either stimulus-driven or goal-directed attentional orienting. Based on their behavioral profile, patients were sorted into groups and their lesion overlap was explored (**Figure 2A**). Patients who exhibited difficulties with goal-directed attentional orienting, as quantified by the top-down attentional index (**Figure 2B**), presented with lesion overlap centered over superior portions of the parietal lobule (subsuming SPL) with spared inferior parietal lobule (TPJ). Patients with lesion overlap centered over the inferior portions of the parietal lobule (subsuming TPJ) but spared SPL performed normally on the goal-directed orienting task, while remaining immune to attentional capture (**Figure 2C**). The findings from this study clearly suggest that SPL and TPJ are anatomical regions that are necessarily recruited for the purposes of top-down and bottom-up orienting and that damage to SPL and TPJ leads to disorders of top-down and bottom-up orienting respectively.

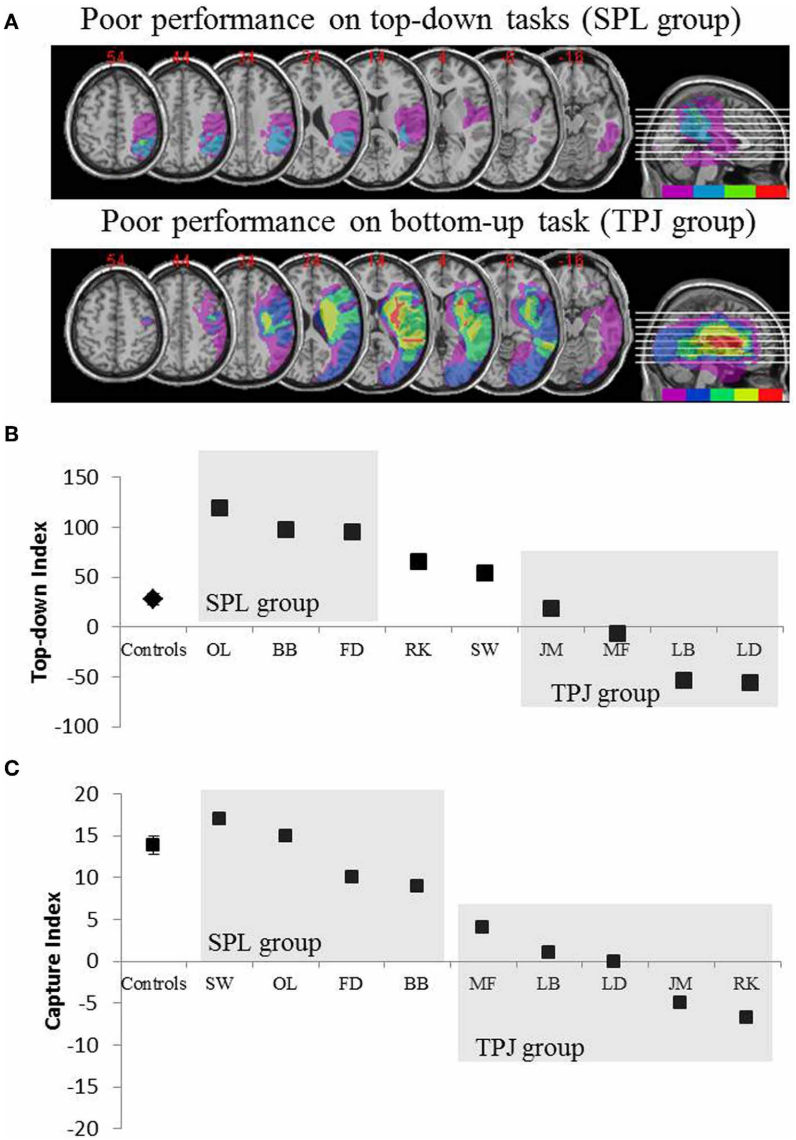

FIGURE 2 | Results of the neuropsychological study aimed at investigating the relative contribution of SPL and TPJ to top-down and bottom-up orienting. (A) Lesion overlaps (purple minimal overlap; red maximal overlap) for patients grouped by behavioral deficits in top-down attentional orienting, labeled the SPL group (top panel); and patients grouped by behavioral deficits in bottom-up orienting, labeled the TPJ group (lower panel). **(B)** Behavioral performance on the top-down task summarized with a "Top-down Index" which quantifies differences between spatial top-down shifts made from left to right and vice versa. Controls and the TPJ lesioned group show similar efficiencies in executing spatial shifts, while patients with SPL lesions show decreased efficiency. Group control and individual patient data (labeled with patient initials) are plotted on the abscissa. **(C)** "Capture index" is a measure of bottom-up attention and quantifies the extent to which task-irrelevant distractors capture attention away from the task. Controls and the SPL lesioned group show similar capture values, such that both groups are captured by the task-irrelevant distractors. TPJ lesioned group show much reduced capture index (failure to be captured). Note that patients were placed in the SPL or TPJ group based on behavior, rather than based on the lesion, thus note the consistency with which patients end up in the corresponding group.

INTERACTION BETWEEN TOP-DOWN AND BOTTOM-UP SELECTION

Although there is apparently a strong association between goal-directed orienting and SPL and stimulus-driven orienting and TPJ, data from Shomstein et al. (2010) patient study suggest that these two systems are not entirely independent. This conclusion is supported by the finding that patients with SPL damage exhibited a pattern of performance labeled as "hyper capture." Unlike controls, for whom only target colored distractor captured attention (leading to lower target accuracy), irrelevant colored distractors also proved to be distracting for patients with SPL lesion. In addition, whereas for controls attention was captured by distractors only when they preceded the onset of the target, for patients with SPL lesions attention was even captured by distractors presented

simultaneously with the target. This pattern of performance can be explained by the following framework: SPL is responsible for top-down guidance of attention that includes determining the aspects of the stimuli that are task relevant (e.g., search for red target; Corbetta and Shulman, 2002; Serences et al., 2005). This attentional set then constrains TPJ, such that the capture of attention mechanism that is mediated by TPJ is only triggered by the task relevant information (e.g., red distractors capturing attention, and gray distractors not capturing attention when searching for a red target). The absence of SPL prevents the establishment of a task relevant attentional set and thus any stimulus, task relevant or not, is deemed important therefore capturing attention (e.g., task-irrelevant distractor capturing attention for the SPL group) indiscriminately.

It has been suggested that SPL and TPJ could interact in at least one of two possible ways. The first possibility is that TPJ serves as an alerting system that detects behaviorally relevant stimuli but lacks the high spatial resolution, thus when a behaviorally relevant stimulus is detected its precise location is supplied by the SPL that stores spatial maps (Kastner et al., 1999; Wojciulik and Kanwisher, 1999; Bisley and Goldberg, 2003; Silver et al., 2005). A related hypothetical possibility is that the capture mechanism (that includes TPJ) acts as a circuit breaker of ongoing cognitive activity when a behaviorally relevant stimulus is presented (Corbetta and Shulman, 2002, 2011). The "hyper-capture" pattern of activity observed in patients with preserved TPJ but lesioned SPL provides further evidence for the hypothesis that views TPJ as issuing a control signal that terminates the task at hand thus serving as a circuit breaker (Corbetta and Shulman, 2002; Serences et al., 2005). Other recent neuroimaging studies employing various paradigms have provided further evidence for an interactive relationship between the top-down and the bottom-up attentional orienting, and subsequently for the relationship between SPL and TPJ (Serences et al., 2005; Asplund et al., 2010; Diquattro and Geng, 2011).

While the evidence for an interaction between the two attentional systems and the two attentional substrates (SPL and TPJ) is strong, what remains unclear is whether this interaction is direct between SPL and TPJ or whether it is accomplished through other intermediary regions. As was mentioned earlier, top-down and bottom-up attentional orienting networks engage various regions within the frontal cortex, thus it is reasonable to hypothesize that the convergence between the two systems might be accomplished via the frontal lobe. Two recent studies investigating the interaction between top-down and bottom-up attentional selection provided evidence for the IFJ and IFG as possible sites of convergence between stimulus-driven and goal-directed selection (Asplund et al., 2010; Diquattro and Geng, 2011). The IFJ and IFG appear to be ideal candidates for such interaction given their general involvement in attention and cognitive control as well as its involvement in both spatial and non-spatial selection (Koechlin et al., 2003; Brass et al., 2005).

THE ROLE OF THE PARIETAL LOBE IN TOP-DOWN AND BOTTOM-UP SELECTION: PHYSIOLOGY

While the emphasis of this review has been predominantly placed on human studies, a great wealth of knowledge about the involvement of parietal cortex in attentional orienting has been gleaned from monkey physiology investigations (see recent review by Bisley and Goldberg, 2010). However, when it comes to examining the relative contributions of different regions within the parietal cortex to top-down and bottom-up attentional orienting, monkey physiology literature falls short. The primary reason for this is that within the monkey cortex there does not appear to be evidence for the same segregation of top-down and bottom-up control. Instead, lateral intraparietal area (LIP) originally thought to be involved in saccade planning (Gnadt and Andersen, 1988) is involved in visual attention and acts as a priority map in which external stimuli are represented according to their behavioral priority derived in either top-down or bottom-up manner (Colby and Goldberg, 1999; Bisley and Goldberg, 2003, 2010; Balan and Gottlieb, 2006; Ipata et al., 2006; Buschman and Miller, 2007; Gottlieb and Balan, 2010).

CONCLUSION

Although much less is known about human parietal cortex than that of homologous monkey cortex, recent studies, employing neuroimaging and neuropsychological methods, have begun to elucidate increasingly fine-grained functional and structural distinctions. This review focused on recent neuroimaging and neuropsychological studies elucidating the cognitive roles of dorsal and ventral regions of parietal cortex in top-down and bottom-up attentional orienting, and on the interaction between the two attentional allocation mechanisms.

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