PEARCE-HALL ATTENTION FOR LEARNING PARAMETER: MEMORY SUBSTRATES

by
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Abstract

This thesis expands our characterization of brain circuits that implement attention to facilitate learning according to Pearce & Hall (1980) rules. In the Pearce & Hall (1980) model, the *dynamic attention parameter* (α) is the variable that determines the selection of cues to learn about. For every registered cue, the value of α is adjusted towards the amount of contemporaneous surprise (prediction error), and then stored in memory. Considerable work by Holland, Gallagher & associates revealed the existence of an amygdalo–nigral–cortical circuit that underlies the encoding and expression of α. In each of the 8 experiments in this thesis, rats were trained in a serial prediction task, and intraparenchymal microinfusions of transient action pharmacological agents were delivered at separable stages of α memory processing. The first three experiments establish posterior parietal cortex (PPC) as a candidate storage locus by demonstrating its importance during α encoding, consolidation, and expression. The next experiment dissociated the roles PPC and adjoining secondary visual cortex (V2) during encoding, and the subsequent experiment revealed V2 to be a novel component of the α expression module. The three final experiments suggested a role for amygdala central nucleus (CeA) in modulating α memory consolidation. Circuit implications are discussed throughout.

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For now, I thank you committee members.

And of course, I thank the Good Dr.

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Chapter 1:

General Introduction

Through associative learning, organisms build and amend an internal representation of the dynamics of their environment (Tolman, 1932; Zener, 1937; Dickinson & Mackintosh, 1978; Rescorla, 1978; 1988a). An implicit goal of this process is the reduction of uncertainty about the occurrence of events by obtaining knowledge about the predictive relationships between events (Rescorla, 1972; Dayan & Abbott, 2010). Thus, the surprising occurrence of some significant event informs an organism of its ignorance about predictors for that event; its current model of the world is inaccurate or incomplete and should be updated (Rescorla, 1988b). Multiple learning mechanisms are capable of rectifying gaps in the world model. In the next section, I mention three (Rescorla & Wagner, 1972; Mackintosh, 1975; Pearce & Hall, 1980; c.f. Widrow & Hoff, 1960; Kalman, 1960; Frey & Sears, 1978), whose elements have since been recast or integrated into more contemporary frameworks (e.g. Schmajuk et al., 1996; Dayan et al., 2000; Kruschke, 2001; LePelley, 2004; Courville et al., 2006; Pearce & Mackintosh, 2010; Haselgrove et al., 2010; Esber & Haselgrove, 2011). I provide a cursory description of the function of surprise in each of those classic theories, and I do not enumerate their merits and limitations (see Sutton & Barto; 1981; Miller et al., 1995; Pearce & Bouton, 2001; LePelley, 2010; Schmajuk, 2010).

Rescorla-Wagner (1972) model

Mounting evidence of the insufficiency of temporal contiguity for conditioning (e.g. Rescorla, 1967; Kamin, 1968; 1969) stimulated a paradigm shift in animal learning theory (Dickinson, 1980; Mackintosh, 1983; Schmajuk, 1997; 2010). Undoubtedly, the most influential model that emerged was that of Rescorla & Wagner (1972), which parted from predecessors (e.g. Hull, 1943; Bush & Mosteller, 1951) by stipulating a composite prediction of events. Actual events are compared against that composite, and the ability of those actual events to alter the composite is gated by their unexpectedness. That is, in RW, the extent of surprise determines the reinforcing power of a surprising event.

Mackintosh (1975) model

Sutherland & Mackintosh (1971) underscored the limited capacity of attention as the primary constraint on learning. Shortly thereafter, Mackintosh (1975) formulated that notion with a stimulus selection mechanism by which more attention is paid towards appropriate cues to facilitate learning about relevant features in the environment. In MK, appropriate cues are the best available predictors of significant events, and the best predictor is a stimulus (complex) that minimizes surprise relative to all other available predictors. Thus, surprise signals the inadequacy of stimuli as predictors, and encourages shifts of attention away from those stimuli and towards better predictors, should they exist.

Pearce-Hall (1980) model

However, surprise may also signal opportunities to procure new information (Dickinson, 1980; Itti & Baldi; 2009; Gottlieb et al., 2013). We invoke this latter notion when

referring to the Pearce & Hall (1980) mechanism of attention for learning as a glutton for information. Surprise whets the appetite of an information-seeker, and PH assumes that salient events preceding or accompanying a surprising one are likely sources of information about it. Namely, in PH, a surprising event biases the future allocation of attention towards contiguous events, which we call cues, during subsequent encounters with those cues to accelerate the reduction of uncertainty about the occurrence of the surprising event. Importantly, while the purpose may be to eliminate that particular surprise (and fill the world-model gap), the lingering attentional bias in PH facilitates learning about any predictive relationship involving those cues. Perhaps instead of seeking to find predictors for a surprising event so that it can become expected, PH seeks to determine the predictive significance of cues (information they provide about the occurrence of other events), and surprise indicates the potential for such discovery (Dickinson, 1980).

In the Pearce-Hall framework, as in others, cues compete for access to the limited-capacity associative learning process. In PH, selection of cues for access depends upon the combination of two factors: (1) the physical aspects of stimuli, hereby referred to as *cue salience* (*S*) to adhere somewhat to the convention of cognitive neuropsychological models of attention (Koch & Ullman, 1985; Treisman, 1988), and (2) the extent that stimuli were followed by surprising events in the past. The uncontroversial inclusion of *S* accounts for such banality as the observation that a loud sound is learned about more readily than a much quieter one. The second factor interests us, and PH part from RW and MK in their description of the effect of surprise. Specifically, in PH, the value of the *dynamic attention parameter* (α) for each cue gradually approaches the magnitude of contemporaneous aggregate

error ($\alpha \approx |\lambda - \sum V_X|$ where λ represents an actual event and $\sum V_X$ represents an expectation of that event given the set X of available cues). All else equal, cues with greater α values garner more attention and therefore achieve privileged access to the associative learning process than those with lesser α values. In the simplest conceptualization of PH, computations of surprise update α values, and updated α values (along with *S*) subsequently determine the selection of cues to be learned about. Although jejune, this summary conveniently organizes the demands of a task we use to study the neural basis of separate stages of α memory processing: encoding, storage, and expression.

Table 1. Serial Prediction Task Design

Behavioral condition	Expectancy phase 10-15 sessions	Surprise phase 2 sessions	Test phase 5 sessions
Shift	8 x Light → tone → food 8 x Light → tone → nothing	8 x Light → tone → food 8 x Light → nothing	16 x Light → food
Consistent	8 x Light → tone → food 8 x Light → tone → nothing	8 x Light → tone → food 8 x Light → tone → nothing	16 x Light → food

Pearce-Hall networks and the serial prediction task

In PH, to reconcile $\alpha_{stimulus}$ values with experience, computational networks generate a prediction given registry of a stimulus, determine the inaccuracy of that prediction, then adjust the value of $\alpha_{stimulus}$ to bias attention towards future opportunities for learning. The design of the serial prediction task (Table 1), originated by Wilson et al., (1992) (c.f. Holland et al., 2002), permits independent assessment of α memory processing stages by widely separating episodes when α_{Light} values diverge between groups (*surprise phase*) from those when divergent α_{Light} values are expressed to produce measurable differences in learned behavior (*test phase*). In the first phase (e*xpectancy*), all rats are exposed to serial light→tone

pairings across many days. As rats come to expect the tone given the light, α_{Light} gradually decreases. Next, in the surprise phase, the light stimulus prompts anticipation of the tone, but the tone is omitted on some trials for one group of rats (shift), while the other group (consistent) continues to receive the same light→ tone pairings. Since the absence of an expected stimulus, in this case the tone, is a surprising event, α_{Light} increases for the shift group during the surprise phase while remaining low for the consistent group. Finally, in the test phase, we begin delivering food immediately after each presentation of the light and measure the acquisition of conditioned food-cup approach. Typically, superior acquisition by the shift group reifies the normative α_{Light} divergence incurred between groups during the previous phase, an effect hereby termed the *shift group advantage*. That advantage depends critically upon the integrity of PH network function.

The latter two phases of the serial prediction task impose distinct demands upon PH networks. During the surprise phase, rats (1) register the light, (2) retrieve an expectation about the occurrence of the tone, (3) assess the extent of divergence between that expectation of tone and reality, i.e. compute prediction error or surprise, (4) use that surprise computation to adjust α_{Light} values accordingly, and (5) archive updated α_{Light} in memory. Each of these steps is vulnerable to disruption by neural dysfunction, but by completing those steps, shift group animals store greater α_{Light} values in memory than consistent group animals. For the shift group advantage to be observed in the test phase, shift group rats must (1) register the light, (2) retrieve the surprise-increased α_{Light} values from memory, and (3) use those increased α_{Light} values to enhance the allocation of attention to the light and thereby facilitate learning about its predictive relationship with food.

Neural basis of α modulation

Holland, Gallagher and associates constructed a compelling argument for a PH attention system comprised of separable and independent circuits that diverge by supporting either decrements or increments in α (reviewed in Holland & Maddux, 2010). Using a variety of selective neurotoxic lesions and behavioral procedures, it was demonstrated that the hippocampus and its cholinergic innervation is critical only for α decrements (Han et al., 1995; Baxter et al., 1997; 1999a; 1999b; Holland & Fox, 2003), while functioning of amygdala central nucleus (CeA) and cholinergic neurons in substantia innominata/nucleus basalis magnocellularis (SI/nBm) are critical only for increments. Moreover, CeA-dependent processes enhance excitatory and inhibitory learning, but the necessity of an intact CeA appears limited to situations of overexpectation or omission errors (Holland & Gallagher, 1993a; Holland & Gallagher, 1993b; Holland & Kenmuir, 2005; Holland, 2006)

A particularly fruitful line of research on PH neural circuitry trained rats with the serial prediction task (Wilson et al., 1992). The line began when Holland & Gallagher (1993a) found that bilateral neurotoxic lesions of the CeA prevented the enhanced rate of light-food learning that was observed following sham lesions. Additional circuit components were then discovered. It was reasonable to target cholinergic neurons in SI/nBm as the cholinergic hypothesis of dementia had gained prominence, and it had long been suspected that those neurons modulate cortical processing through their widespread innervation of the cortical mantle (Mesulam et al., 1983, Dunnett et al., 1991; Gallagher & Holland, 1994). Additionally, through measurements of cortical EEG, contemporaneous work by Bruce Kapp's lab suggested that the "characteristic searching or attention response" induced by amygdalar

stimulation (Ursin & Kaada, 1960) was mediated by SI/nBm (Kapp et al., 1994; Whalen et al., 1994). Rat basal forebrain cholinergic neurons could be targeted with greater precision following advent of an immunotoxin selective against them, 192 IgG-saporin (Wiley et al., 1991; Book et al., 1992). Pre-training infusions of the immunotoxin into SI/nBm disrupted the shift group advantage (Chiba et al., 1995), and cholinergic deafferentation of posterior parietal cortex (PPC) produced similar impairments (Bucci et al., 1998). Application of the asymmetrical lesion approach revealed that the shift group advantage required ipsilateral operation of CeA and cholinergic SI/nBm (Han et al., 1999), and CeA and substantia nigra pars compacta lateralis (SNcl) (Lee et al. 2006; 2008). Finally, functions of CeA and SI/nBm were doubly dissociable. Transient pharmacological perturbations suggested that CeA activity mattered during α encoding, but not expression, while SI/nBM activity mattered during α expression, but not encoding (Holland & Gallagher, 2006). From these findings, Holland & Maddux (2010) describe a circuit model that separates components into two modules: one that relies upon cooperation of CeA and SNcl to increase the value of α_{Light} following the surprising omission of the tone, and the other that requires cholinergic innervation of PPC by SI/nBM to accelerate test phase light-food learning through the expression of increased α_{Light} values that were encoded and stored in memory during the surprise phase. The circuit model is agnostic about a substrate that stores increased α_{Light} values between the surprise and test phases.

The next three chapters compel additions to the model. In each experiment of those chapters, rats were trained in the serial prediction task and intraparenchymal microinfusions of transient action pharmacological agents were delivered at separable stages of α_{Light} memory

processing. In the first empirical chapter, I briefly convey the plausibility of PPC as a constitutive storage locus of α_{Light} memories, report evidence in support of that claim, then offer a parsimonious means to connect PPC with the encoding and expression modules (Schiffino et al., 2014). The next chapter demonstrates that intact function of secondary visual cortex (V2) is important for the expression of α_{Light}, but not to encode its increased value, thereby dissociating PPC and adjoining V2 roles in α_{Light} memory processes. Those findings are discussed in the context of attention networks, and neural interactions that may mediate attention facilitated learning are described (Schiffino & Holland, *in prep*). The last empirical chapter reveals the importance of CeA function during the consolidation of α_{Light}. I generalize those results to amygdalar modulation of consolidation and advocate complimentary roles for its nuclei (Schiffino & Holland, *in prep*). A summary of each experiment can be found in Table 2.

Theories in contemporary cognitive neuropsychology frame the control of selective attention as an assembly and subsequent read-out of 'priority maps' of parameter space (Serences & Yantis, 2006). These priority maps integrate across exogenous stimulus properties (c.f. *saliency map* of Koch & Ullman, 1985; Itti & Koch, 2000; 2001) and endogenous (e.g. motivational state) factors to dictate the deployment of attention (Baluch & Itti, 2011; Itti & Borji, 2014). The α construct represents a factor that gains prominence when an organism endeavors to solve the relational structure of their environment through learning about contingencies between events (cf. Pearce & Hall, 1980; Dickinson, 1980; Pearce et al., 1982; Dayan et al., 2000; Schultz & Dickinson, 2000; Yu & Dayan, 2005; Courville et al., 2006; Baldi & Itti, 2010; Wilson et al., 2010; Nassar et al., 2010; 2012;

Gottlieb, 2012; Iglesias et al., 2013; O'Reilly et al., 2013; Gottlieb et al., 2013; Payzan-LeNestour et al., 2013; McGuire et al., 2014).

Table 2. Summary of Experiments

Chapter	Cannulated area	Drug Treatment
2	posterior parietal cortex	Experiment 1 NBQX or vehicle prior to Surprise sessions Experiment 2 NBQX or vehicle prior to Test sessions Experiment 3 Anisomycin immediately after Surprise sessions and vehicle 24 h later (Immediate) or vehicle immediately after and anisomycin 24 h later (Delayed)
3	extrastriate cortex	Experiment 4 NBQX or vehicle prior to Surprise sessions Experiment 5 NBQX or vehicle prior to Test sessions
4	central nucleus amygdala	Experiment 6 Anisomycin immediately after Surprise sessions and vehicle 24 h later (Immediate) or vice versa (Delayed) Experiment 7 Lidocaine immediately after Surprise sessions and vehicle 24 h later (Immediate) or vice versa (Delayed) Experiment 8 Muscimol immediately after Surprise sessions and vehicle 24 h later (Immediate) or vice versa (Delayed)

Chapter 2:

Posterior Parietal Cortex and α_{Light} Storage

Introduction

PPC is a critical component of attention networks (Mesulam, 1981; Posner & Petersen, 1990; Desimone & Duncan, 1995; Coull, 1998; Kastner & Ungerleider, 2000; Corbetta & Shulman, 2002; Reep & Corwin, 2009; Petersen & Posner, 2012). Patients with damage to the PPC show deficits in visuospatial attention, including spatial neglect (Critchley, 1953; Corbetta & Shulman, 2011), and transcranial PPC stimulation has been used to ameliorate those deficits (Shindo et al., 2006; Ko et al., 2008; Song et al., 2009; Sparing et al., 2009) as well as to enhance the rate of new learning in healthy adults (Iuculano & Cohen-Kadosh, 2013).

Subdivisions of primate PPC, specifically the intraparietal sulcus (IPS) in humans and the homologous lateral intraparietal area (LIP) in macaques (Grefkes & Fink, 2005), supply visuospatial priority maps to direct the deployment of attention (Serences & Yantis, 2006; Bisley & Goldberg, 2010; Baluch & Itti, 2011; Gottlieb, 2014). Functions of rat PPC appear analogous to those of primates, including in mediating the control of attention (Kolb & Walkey, 1987; Corwin & Reep, 1998; Whitlock et al., 2008; Reep & Corwin, 2009; Broussard, 2012; Nitz, 2014; Raposo et al., 2014; Hanks et al., 2015). Importantly, when animals seek to learn, stimuli with uncertain relationships are given priority over others in part through activity of PPC (subdivisions) (Holland & Maddux, 2010; Gottlieb, 2012; Gottlieb et al., 2013). Although the engram for determining that priority, which α represents, is unknown,

parameters for the control of attention are likely stored within networks associated with its control (c.f. Summerfield et al., 2006; Danker & Anderson, 2010; Stokes et al., 2012; Kuhl & Chun, 2014; Capotosto et al., 2015). Since PPC is an integral component of rat attention networks (Corwin & Reep, 1998; Reep & Corwin, 2009; Bucci, 2009; Broussard, 2012), it is plausible that the region contributes to the storage α memories.

That rationale was buttressed by two studies that trained animals in the serial prediction task (Bucci et al., 1998; Bucci & MacLeod, 2007). First, Bucci et al. (1998) found that the selective removal of cholinergic input through pretraining 192 IgG-saporin infusions into rat PPC prevented the shift group advantage. Corticopetal cholinergic input to PPC predominately originates from neurons in SI/nBM (Bucci et al., 1999), a cell group whose intact activity is necessary for the expression, but not encoding, of α_{Light} memories (Holland & Gallagher, 2006). Conjoint evidence from those studies suggested a role for PPC during α_{Light} expression. Correlational data reported by Bucci & MacLeod (2007) implicated PPC during α_{Light} encoding: when animals were sacrificed shortly after surprise phase sessions, shift group rats expressed increased levels of Fos in PPC relative to consistent group rats. The importance of PPC for encoding, storage, and retrieval of α_{Light} memories therefore merited examination.

Here, in three experiments, we began that assessment through PPC infusion of drugs before surprise phase sessions (encoding), after surprise phase sessions (consolidation), or before test phase sessions (expression). Experiment 1 investigated the importance of unperturbed PPC activity for the encoding of increased α_{Light} values through bilateral infusions of a competitive AMPA-type glutamate receptor antagonist (NBQX) prior to both

surprise phase sessions. Experiment 2 infused NBQX prior to each of the five test phase sessions to assess the necessity of intact PPC function for the expression of surprise-increased α_{Light} values. Experiment 3 probed the involvement of PPC during the consolidation of increased α_{Light} memories through infusions of a translational inhibitor (anisomycin) immediately after surprise phase sessions. Memory consolidation canonically requires *de novo* protein-synthesis and is susceptible to interference by mechanisms of anisomycin action (Davis & Squire, 1984; Bailey & Kandel, 1993; Martin et al., 2000; Kandel, 2001; Dudai, 2004; Dudai & Eisenberg, 2004; Sutton & Schuman, 2006; Alberini, 2008; Costa-Mattioli et al., 2009; Kandel et al., 2014; but see Sharma et al., 2012; Ziv & Fisher-Lavie, 2014; Rosenberg et al., 2014).

Methods

Subjects. Male Long-Evans rats (Charles River Laboratories, Raleigh, NC, USA) were used in this study: 36 in experiment 1, 36 in experiment 2, and 40 in experiment 3. Rats weighed 300-325 g upon arrival at the laboratory vivarium, and were given about 1 week of free access to food and water prior to surgery. Surgery was followed by 10-14 days of recovery before behavioral training. During the recovery period, the rats were handled for at least 2 min each day. After recovery, they were food restricted to reach and subsequently maintain 85% of their free-feeding weights throughout the course of the study. Rats were individually housed in a colony room with a 12:12-h light:dark cycle. The care and experimental treatment of rats were conducted according to the National Institutes of Health's Guide for the Care and Use of Laboratory Animals, and protocols were approved by the Johns Hopkins University Animal Care and Use Committee.

Apparatus. The behavioral training apparatus consisted of four separate chambers (22.9 9 20.3 9 20.3 cm). Each chamber had aluminum front and back walls, clear acrylic sides and top, and a floor of stainless steel rods (0.48 cm in diameter spaced 1.9 cm apart). A recessed food cup was located in the center of the front wall at 2 cm above the floor, and was fitted with phototransistors to detect head entries. Two 45-mg sucrose pellets (Formula 5TUT, Test Diets, St Louis, MO, USA) delivered to the food cup served as the reinforcer. The light conditioned stimulus (CS) was generated by illumination of a 6-W panel lamp with a translucent covering, mounted 15 cm directly above the food cup. A 1500-Hz, 80-dB tone CS was presented via a speaker mounted on the inside wall of a sound-attenuating box that surrounded each chamber.

Surgery. Rats were anesthetized with 2-3% isoflurane mixed with oxygen and placed into the stereotaxic apparatus (Model 902, Kopf, Tujunga, CA, USA). After incision and craniotomy, four 1/8-inch self-tapping mounting screws were installed into the skull. The dura was then punctured with a 27-gauge needle, and a 26-gauge guide cannula (PlasticsOne, Roanoke, VA, USA), with stainless steel tubing cut to extend 3.5 mm below the 8.0-mm-long pedestal, was implanted into each PPC at -4.1 mm posterior and ±3.1 mm lateral to bregma, to a depth of 0.9 mm below the skull surface. The coordinates were chosen in accordance with previous definitions of rat PPC location based on proposed hodological and functional analogies with the human and nonhuman primate PPC (Burcham et al., 1997; Corwin & Reep, 1998; Bucci et al., 1999; Reep & Corwin, 2009). Cannulas were held in place with dental acrylic and fitted with obturators that were cut to match the length of the guide. Once the acrylic set, the incision was closed with surgical staples and topical antibiotic

ointment was applied to the wound edges. All rats then received subcutaneous injections (0.02 mg/kg) of sterile buprenorphine HCl (Sigma, St Louis, MO, USA) to ameliorate pain.

Behavioral training procedures. Table 1 provides an outline of the behavioral training procedures. Once their weights reached 85%, rats were first given 10 sucrose pellets in their home cages, to familiarize them with the reinforcer. Each 64-min behavioral training session in each phase of the experiments included 16 trials, distributed across random intertrial intervals, which averaged 4 min (range 2–6 min). The rats were first trained to eat sucrose pellets from the recessed food cups, in a single session, which included 16 unsignaled reinforcer deliveries. Then, to establish a strong light–tone association during the expectancy phase, all rats received trials consisting of a 10-s light → 10-s tone serial compound. In each session of this phase, half of the 16 trials had the light → tone compound reinforced with sucrose pellets and the other half were not reinforced. The trial order in each session was randomly determined. After 15 sessions of expectancy training, rats were allocated to performance-matched shift and consistent groups, and given two surprise phase sessions. During each surprise session, light → tone prediction error was induced for the shift rats by omitting the tone on the eight nonreinforced trials, whereas consistent rats had their light → tone expectancies confirmed through continuation of the expectancy protocol. Finally, in each of the five sessions in the test phase, all rats received 16 presentations of the light CS alone followed immediately by sucrose pellet reinforcement. Greater acquisition of food-cup responses to the light CS was taken as evidence of relatively greater α_{Light} values.

Behavioral measure and analysis. The response measure was the percentage of time spent in the food cup, as assessed by interruption of the infrared photobeam. Trial epochs were

defined as a 5-s stimulus-free pre-CS period (immediately prior to the light CS), the first 5 s of the light CS, the second 5 s of the light CS, the first 5 s of the tone CS, the last 5 s of the tone CS, and the 5 s initiated by reinforcer delivery. Conditioned food-cup responding was assessed during the latter half of CS presentations because, in that epoch, food-cup conditioned responses are more frequent and less contaminated by conditioned orienting behaviors (Holland, 1977).

Responding during the pre-CS, light, and tone (when applicable) epochs were each analyzed with separate analyses of variance (ANOVAs) with behavioral condition (shift or consistent) and drug treatment (NBQX or saline in experiments 1 and 2; immediate-anisomycin or delayed-anisomycin in experiment 3) as between-subject variables, and repeated measures on the within-subjects variable of session blocks (1-5). The Greenhouse-Geisser procedure was used to correct for violations of sphericity. The ANOVAs on test phase data were accompanied by planned contrasts to evaluate the hypotheses that behavioral condition groups differed within each drug treatment (e.g. shift-vehicle vs. consistent-vehicle; shift-NBQX vs. consistent-NBQX) and that drug treatment groups differed within each behavioral condition (e.g. shift-vehicle vs. shift-NBQX; consistent-vehicle vs. consistent-NBQX).

Drugs and infusion procedures. In each experiment, rats had their obturators removed and reinserted either before (experiments 1 and 2) or after (experiment 3) each of the expectancy sessions, to familiarize them with manipulation of their headstages. Two 33-gauge injector cannulas that extended 0.4 mm below the tip of the guide were connected by PE50 tubing to separate 10-μL Hamilton syringes in a multiple-syringe pump (KD Scientific, Holliston, MA, USA). The pump simultaneously administered 0.5 μL of infusate bilaterally

into the PPC, over one minute. After infusion, the injector was left in place for an additional minute. The obturators were reinserted after removal of the injectors. In experiments 1 and 2, PPC activity was disrupted by infusions of 1,2,3,4-tetrahydro-6-nitro-2, 3-dioxo-benzo[f]quinoxaline-7-sulfonamide (NBQX), a competitive antagonist at ionotropic AMPA-type glutamate receptors (Sheardown et al., 1990). NBQX (Sigma) was dissolved at a concentration of 20 μg/μL in 0.1 M phosphate-buffered saline vehicle (El-Amamy & Holland, 2006; Holland & Gallagher, 2006; Lee et al., 2008). Infusions of NBQX were delivered within 20 min prior to the onset of each surprise session (experiment 1) or each test session (experiment 2). Control rats in each training condition received infusions of the phosphate-buffered saline vehicle only. Anisomycin was used to inhibit translation in experiment 3. Anisomycin, (2R,3S,4S)-2-(4-methoxybenzyl)-3,4-pyrrolidinediol-3-acetate, is produced by *Streptomyces griseolus* and reversibly inhibits translation in eukaryotic cells by preventing aminoacyl-tRNA from binding to the A-site of the peptidyl transferase center on 60S ribosomal subunits, thereby hindering peptide bond formation and precluding the elongation of polypeptide chains (Barbacid & Vazquez, 1974; Garreau de Loubresse et al., 2014). Anisomycin (Sigma) was dissolved into HCl at a concentration of 62.5 μg/μL in 0.9% saline vehicle and the pH was adjusted to 7.2. Rats in the 'immediate' drug treatment received infusions of anisomycin immediately after the end of each surprise session, whereas rats in the 'delayed' condition received vehicle-only infusions at these times. To control for lasting side-effects of anisomycin that include ribotoxic apoptosis (Iordanov et al., 1997; Shifrin & Anderson, 1999; Rudy, 2008; Radulovic & Tronson, 2008), the delayed rats also received anisomycin infusions, but at 24 h after each surprise session (c.f. Wanisch & Wotjak, 2008). Rats in the immediate condition received vehicle-only infusions at these (24-h

delay) times. Thus, each rat received two anisomycin and two saline vehicle infusions in the surprise phase, but the rats in the immediate drug treatment received anisomycin at a time when the consolidation of memories acquired during the surprise sessions was more sensitive to interference. Note that, to accommodate this balanced treatment of rats in the immediate and delayed conditions, in experiment 3 all rats were given a day off from behavioral training after each surprise session.

Histological procedures. After the completion of behavioral testing, the rats were deeply anesthetized with sodium pentobarbital (100 mg/kg) and perfused intracardially with 0.9% saline followed by 3.7% formalin solution. After removal of the headstage, the brains were removed and stored at 4°C in 3.7% formalin/12% sucrose solution. Brains were sliced on a freezing microtome and 40-μm coronal sections were taken in series. To confirm cannula tip placements in the bilateral PPC, every third section was mounted on glass slides, dehydrated in ascending concentrations of alcohol, defatted in xylene, and stained with thionin. Slides were coverslipped using Permount thinned with xylene, and examined with a light microscope.

Results

Histological results. Of the 112 rats acquired for the study, the data from 16 were excluded. In experiment 1, five of the 36 rats were excluded because their headstages detached, one rat was removed due to infectious lesion of the PPC, and one rat died during surgery. In experiment 2, one of the 36 rats was excluded after its headstage detached, three rats were removed due to infectious lesion of the PPC, and one rat died during surgery. In experiment 3, one of the 40 rats was excluded after its headstage detached, two rats were

removed due to infectious lesion of the PPC, and one rat was excluded for missed cannula placement. Assessments of cannula tip placements confirmed that PPC was the site of injection for all rats whose data were included for behavioral analyses (Figure 1). In experiment 1, the final numbers of rats in the shift-NBQX, shift-vehicle, consistent-NBQX, and consistent-vehicle conditions were 6, 9, 7, and 7, respectively. In experiment 2, those sample sizes were 8, 8, 7, and 8, respectively. In experiment 3, the final numbers of rats in the shift-immediate, shift-delayed, consistent-immediate, and consistent-delayed conditions were 9, 9, 8, and 10, respectively.

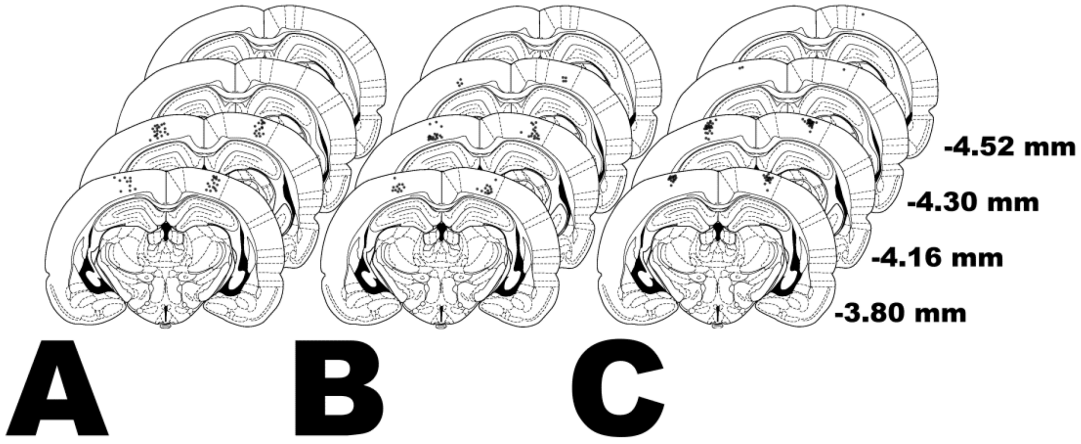


Figure 1. Schematic Representation of Injector Cannula Tip Placements for Rats Included in Experiment 1(A), Experiment 2(B), and Experiment 3(C).

The numbers on the right indicate distance (mm) from bregma along the rostrocaudal axis. For each placement, a single black dot of 50% opacity was drawn using Adobe Photoshop. Thus, darker areas indicate greater overlap.

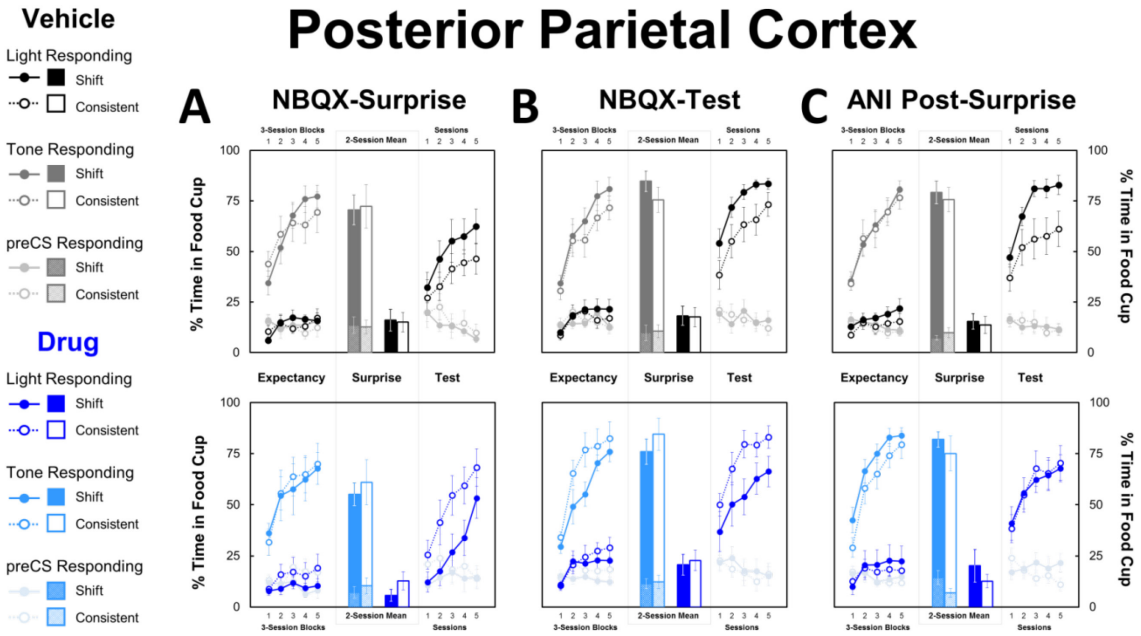


Figure 2. Mean Food-Cup Responding for Experiments 1-3

Mean (± SEM) food-cup responding during pre-CS, light, and tone measurement epochs sequentially across all three phases (expectancy, surprise, and test) of experiment 1 (panel 2A), experiment 2 (panel 2B), and experiment 3 (panel 2C). See the legend for epoch and group (drug treatment x behavioral condition) designations, and see text for statistical results. The heading of each panel identifies the drug treatment (NBQX or ANI) for that experiment and the timing of delivery (pre-surprise, pre-test, or post-surprise, respectively) into PPC. Rats received infusions of vehicle (grayscale; top) or NBQX (shades of blue; bottom) prior to both surprise phase sessions in experiment 1 (2A), or before each test phase session in experiment 2 (2B). In experiment 3 (2C), rats were either infused with anisomycin immediately after each surprise session and then with vehicle 24 h later (blue; drug), or infused with vehicle immediately after each surprise session and then with anisomycin 24 h later (grayscale; vehicle). Analysis of expectancy and surprise phase data did not reveal major caveats: rats acquired and maintained comparably high levels of food-cup responding to the tone while exhibiting minimal conditioning to the light. The right side of each panel depicts the acquisition of food-cup responding over the course of the five test phase sessions

Behavioral results. Figure 2 depicts food-cup responding during pre-CS, light, and tone measurement epochs sequentially across all three phases (expectancy, surprise, and test) of experiment 1 (panel 2A), experiment 2 (panel 2B), and experiment 3 (panel 2C).

Expectancy phase. In each Fig. 2 panel, the leftmost portion shows that within each of the three experiments, all groups of rats acquired comparably high levels of food-cup responding to the tone while exhibiting minimal conditioning to the light. For each experiment, behavioral condition (shift vs. consistent) x subsequent drug treatment (NBQX vs. vehicle in experiments 1 and 2, immediate vs. delayed anisomycin in experiment 3) x three-session block (1-5) ANOVAs were performed on data from each measurement epoch (pre-CS, light, and tone). No significant effects or interactions (*P*s > 0.08) were observed for any variable in any of the three experiments aside from the effect of block on pre-CS responding in experiment 3 ($\varepsilon = 0.69$, $F_{4,128} = 3.85$, $P = .014$) and the pervasive effects of block on responding during the light (*P*s < .004) and tone (*P*s < .001). Additional behavioral condition x subsequent drug treatment ANOVAs of performance over the final two sessions of the expectancy phase also showed no significant main effects or interactions (*P*s > .201). Thus, within each experiment, rats in all groups entered the surprise phase with similar levels of responding.

Surprise phase. The bars in Fig. 2 depict food-cup response means collapsed across the two surprise phase sessions. For each experiment, data from each of the three measurement epochs were subjected to behavioral condition x drug treatment ANOVAs. In experiment 1, some rats from both behavioral conditions received infusions of NBQX prior to each of these sessions, whereas the remaining rats received infusions of vehicle. Importantly, there were no significant effects of drug treatment on pre-CS responding ($F_{1, 25} = 1.34$, $P = 0.258$),

responding during the light ($_{F1, 25}$ = 0.16, P = 0.694), or responding during the tone ($F_{1, 25}$ = 0.90, P = 0.352). Moreover, there were no significant effects of behavioral condition on responding (Ps > 0.703), and the behavioral condition x drug treatment interaction was not significant during any of the measurement epochs (Ps > 0.594).

In experiment 2, rats did not receive infusions of NBQX or vehicle until the test phase, but data from the surprise sessions were analyzed with subsequent drug treatment included as a factor. No effects of subsequent drug treatment (Ps > 0.604) or behavioral condition (Ps > 0.791) were significant for any measurement epoch, nor were their interactions significant (Ps > 0.264). In experiment 3, rats either received infusions of anisomycin immediately after surprise sessions (immediate rats), followed by infusions of vehicle 24 h later, or were infused with vehicle immediately after surprise sessions and infused with anisomycin after 24 h (delayed rats). No effects of subsequent drug treatment (Ps > .409) or behavioral condition (Ps > .324) were significant for responding during either cue, nor did those variables interact (Ps > .585). Thus, within each of the three experiments, rats in all groups began the test phase after showing similar levels of responding to both the light and tone during the surprise phase.

Test phase. The rightmost portion of each Fig. 2 panel shows the primary data of this study, the acquisition of food-cup responding to the light during the test phase. Mixed, repeated-measures ANOVAs of light and pre-CS responding during the test phase included the between-subjects variables of behavioral condition and drug treatment, and the within-subjects variable of test sessions (1–5) with Greenhouse-Geisser correction.

Infusions of NBQX into PPC prior to each surprise phase session in experiment 1 (Fig. 2A) or prior to each test phase session in experiment 2 (Fig. 2B) eliminated the shift

condition advantage in learning about the light. The behavioral x drug interaction was significant for experiments 1 ($F_{1, 25} = 8.30$, $P = 0.008$) and 2 ($F_{1, 27} = 12.37$, $P = 0.002$). The planned comparisons confirmed that the greater responding during the light by shift-vehicle rats relative to the consistent-vehicle rats was significant for both experiment 1 ($P = 0.044$) and experiment 2 ($P = 0.039$), while the apparent difference in the opposite direction for NBQX-infused rats was reliable for experiment 2 ($P = 0.010$) but not for experiment 1 ($P = 0.060$). Importantly, shift-NBQX rats showed significantly reduced responding relative to shift-vehicle rats in experiment 1 ($P = 0.005$) and experiment 2 ($P = 0.010$), whereas the difference between consistent-NBQX and consistent-vehicle rats was not significant for either experiment ($Ps = 0.101$).

In experiment 3 (Fig. 2C), infusions of anisomycin immediately after surprise sessions abolished the shift advantage that was observed in test in control rats, which had received anisomycin infusions at a delay of 24 h after surprise sessions. Although behavioral condition did not interact significantly with drug treatment ($F_{1, 32} = 3.41$, $P = 0.074$), the three-way interaction between those factors and test session was significant ($\varepsilon = 0.75$, $F_{4,128} = 4.62$, $P = 0.005$), indicating that the difference in learning rates for the two behavioral conditions across sessions indeed depended on the timing of anisomycin infusions. Planned comparisons confirmed that, among delayed rats, the enhanced learning by the shift group relative to the consistent group was indeed reliable ($P = 0.035$), but rats that received anisomycin immediately after surprise showed no such advantage ($P = 0.648$). Moreover, for shift animals, the greater learning demonstrated by delayed rats relative to immediate rats was significant ($P = 0.034$), but no reliable difference was observed between drug treatment groups in the consistent condition ($P = 0.686$).

Analyses of pre-CS responding in the test phase did not reveal caveats. The ANOVAs showed that pre-CS responding was not significantly affected by behavioral condition (*P*s > 0.390) or drug treatment (*P*s > 0.118), nor did those variables interact (*P*s > 0.555) in any experiment. The significant main effects of test session in experiment 1 ($F_{4, 100}$ = 3.26, *P* = 0.015) and experiment 2 ($F_{4, 108}$ = 3.53, *P* = 0.010) reflect a gradual decline of pre-CS responding over the course of the test phase, but effect of session was not significant in experiment 3 ($F_{4, 128}$ = 1.54, *P* = 0.194). Importantly, for all experiments, test session did not interact significantly with either behavioral training condition or drug treatment (*P*s > 0.181), nor were the three-way interactions significant (*P*s > 0.172).

Discussion

Previous research from our laboratory identified an amygdalo–nigral–cortical circuit important for the production and expression of surprise-induced increases in α values (reviewed in Holland & Maddux, 2010). Neurons (Calu et al., 2010) in the CeA, including those identified as projecting directly to SNcl (Lee et al., 2010), code the surprising omission of expected events. Furthermore, CeA and SNcl cooperation is critical for increasing the value of α at the time of surprise, but not for the expression of an already-increased α parameter through more rapid subsequent learning (Holland & Gallagher, 2006; Lee et al., 2006, 2008). By contrast, intact innervation of the PPC by cholinergic neurons in the basal forebrain substantia innominata (SI) is necessary for increased α to accelerate learning in test, but is not essential for adjusting that parameter at the time of surprise (Bucci et al., 1998; Holland & Gallagher, 2006).

Importantly, this model lacked a substrate that stores the altered α memory from when it is first incremented by surprise to when it is later retrieved for use in learning. Here, we found that the PPC may be critical for this storage function. Intact PPC function was essential for surprise-induced enhancements of α in the shift condition, both at the time of surprise, when the increased α parameter is initially encoded (experiment 1), and at the time of retrieval of increased α, when it is expressed through behavior as faster learning (experiment 2). Furthermore, the PPC seems to be involved in at least one aspect of the storage process itself, the post-surprise consolidation of the altered α memory. In experiment 3, inhibition of translation in the PPC shortly after surprise sessions prevented the subsequent expression of enhanced learning in the shift condition (but see Rudy, 2008, for alternative accounts of the effects of anisomycin).

Two additional aspects of our data are noteworthy. First, none of our manipulations of PPC function significantly affected the performance of rats trained in the consistent condition. Not only does this observation provide an important control for the effects that we obtained in rats trained in the shift condition, but it also indicates that the PPC is not importantly involved in the reductions in α that are anticipated within the Pearce–Hall model (Pearce & Hall, 1980) as the light comes to predict the tone in the expectancy phase. This finding confirms previous indications that the brain mechanisms for increases and decreases in α are at least somewhat independent; none of our interventions in the amygdalo–nigral–cortical circuit just described affected the performance of rats trained in the consistent condition or in other tasks designed to assess decreases in α. By contrast, lesions (Han et al., 1995) or cholinergic deafferentation (Baxter et al., 1997) of the hippocampus, which interfered with decreases in α in several tasks, including the consistent condition of the task

used here, did not interfere with surprise-induced enhancements of α in rats trained in the shift condition.

Second, in experiments 1 and 2, test responding of rats in the shift condition that received NBQX infusions before surprise or test sessions was lower than that of NBQX-infused rats trained in the consistent condition, as if the omission of the expected tone reduced rather than enhanced α_{Light}. This observation probably reflects other processes of learning and attention that are normally masked by α enhancements in the shift condition. For example, nonreinforced presentations of the light alone in the surprise phase might enhance inhibitory learning to that cue (Rescorla & Wagner, 1972), or produce greater latent inhibition (Lubow & Moore, 1959) than would nonreinforced presentations of that light within the light→tone compound (Mackintosh, 1975; Lubow et al., 1982). Similar effects were reported after lesions of the CeA (Holland & Gallagher, 1993) or SI/nBm (Chiba et al., 1995).

Some cautions remain in interpreting our data. First, although we believe that our infusions targeted the PPC specifically, it is important to recognize that, because our study used visual stimuli, we cannot completely rule out contributions of the adjoining secondary visual cortex to our results. However, note that interference with basic sensorimotor and perceptual processes would probably disrupt performance in all training conditions and not be selective to the shift condition, as observed here. Furthermore, in previous experiments, removal of cholinergic input to the PPC, which disrupted performance in the serial prediction task used here, also disrupted performance in other tasks in which the α values of auditory stimuli was enhanced by surprise (Bucci et al., 1998). Second, although we interpret the results of experiment 1 as indicating that PPC function is critical to the initial encoding

of surprise-altered α, we cannot rule out the possibility that the role of the PPC is limited to post-session processing, a role shown to be important in experiment 3. In that experiment we found that post-session administration of anisomycin disrupted performance, presumably by disrupting consolidation of the altered α memory. Lingering post-session effects of NBQX inactivation may have had a similar effect in experiment 1.

The present results force a reconsideration of the nature of brain circuitry used in the updating, storage and expression of Pearce–Hall α information. Holland & Gallagher (1999) and Bucci et al. (1998) sketched a simple circuit whereby CeA projections to SI cholinergic neurons directly modulate activity of the PPC. However, because the PPC does not receive direct projections from either of the regions known to increase α at the time of surprise (CeA and SNcl), and disrupting basal forebrain cholinergic innervation of the PPC solely at the time of surprise is without effect (Holland & Gallagher, 2006; Schiffino & Holland, unpublished observations), other brain regions must mediate any effects that the CeA and SNcl have on the PPC during the initial encoding of increased α. One route worth considering is a canonical basal ganglia–thalamocortical loop (Alexander et al., 1986), i.e. SNcl could influence PPC through its innervation of caudoputamen, which in turn projects to substantia nigra pars reticulate (SNpr). SNpr sends efferents to PPC-projecting thalamic nuclei, including lateral posterior and lateral dorsal (Deniau & Chevalier, 1992; Sakai et al., 1998; Sakai & Bruce, 2004; Kamishina et al., 2009). An alternate, less circuitous path courses along SNcl projections to the supragenual portion of the anterior cingulate cortex (Emson & Koob, 1978; Lindvall et al., 1978), which innervates PPC and also connects with adjacent medial agranular cortex, a notable PPC afferent important for directed attention in the rat (Reep et al., 1994; Burcham et al., 1997; Reep & Corwin, 2009). Interest in this latter route is

reinforced by electrophysiological, imaging, and computational work suggesting that the anterior cingulate cortex signals prediction errors, including the surprising omission of expected events (Holroyd & Coles, 2002; Rushworth & Behrens, 2008; Totah et al., 2009; Alexander & Brown, 2011; Hayden et al., 2011; but see O'Reilly et al., 2013), and may itself code α (Bryden et al., 2011).

Mechanisms that retrieve the increased α memory ostensibly stored in PPC and allow the expression of that memory to guide attention for learning remain poorly specified. Normal performance in the serial prediction task requires intact function of cholinergic neurons in the SI, including those that project to the PPC, during the expression of increased α at the time of test (Holland & Gallagher, 2006). However, understanding of the role of this PPC cholinergic innervation is incomplete. For example, corticopetal cholinergic release onto the PPC may directly retrieve the α memory, may be required for the PPC α memory to be retrieved by other inputs, may be necessary for transmitting retrieved α information to other portions of attention networks, or may be important for the proper execution of the feedback modulation of the PPC over processing in sensory areas (c.f. Broussard et al., 2009; Zaborszky et al., 1999; Gu, 2003; Sarter et al., 2005; Hasselmo & Sarter, 2011). Alternatively, the SI cholinergic modulation of cortical processing in general (Hasselmo & Sarter, 2011), known to be important in other attentional tasks (e.g. Everitt & Robbins, 1997; Sarter & Bruno, 2000), may itself be modulated by input from the PPC when increased α memories are expressed in learning. In that case, such input would probably be mediated by the medial prefrontal cortex.

Along with direct cortical–cortical interactions (Mesulam, 1981; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000; Corbetta & Shulman, 2002, 2011; Shipp, 2004;

Pessoa & Adolphs, 2010), prefrontal regulation of corticopetal cholinergic release has long been proffered as a potential means for the top-down modulation of attention (Coull, 1998; Zaborszky et al., 1999; Zaborszky, 2002; Sarter et al., 2005, 2006; Fadel, 2011). Perhaps expression of α entails frontoparietal regulation of corticopetal acetylcholine. It has been suggested that modality-specific posterior cortical–prefrontal–basal forebrain–cortical triangular circuits mediate certain physiological aspects of attentional control (Zaborszky, 2002), and results of both pharmacological and electrical stimulation studies are consistent with such predictions (Golmayo et al., 2003; Nelson et al., 2005). Therefore, α information might be retrieved and forwarded by PPC to medial agranular cortex/anterior cingulate cortex and then relayed ventrally through projections to the prelimbic and infralimbic cortices (Hoover & Vertes, 2007), both of which have extensive efferents that synapse onto neurons in SI (Zaborszky et al., 1997). This is merely one route through which α information stored in the PPC could be used to enhance attention for learning, but the importance of these connections, particularly those from PPC to PFC, awaits assessment.

Considerable behavioral data show that the violation of outcome expectancies today alters the course of learning tomorrow. Thus, there must be some relatively permanent memory of the parameters that determine that course. Although previous research explored the initial acquisition and ultimate expression of attentional changes in associative learning, questions of how, when or where memories for such changes might be stored have not been addressed. Whereas neuroscientists and psychologists have searched for the sites and mechanisms of memory for associations between cues and rewards, there has been less concern for how changes in attention to particular cues are represented in memory. Furthermore, attempts to do so have been largely limited to describing changes in aspects of

sensory receptive fields (e.g. Chavez et al., 2009; Bieszczad & Weinberger, 2010). However, these changes alone cannot form the basis for our findings, because the associability of a cue (its ability to participate in new learning) is often not correlated with the likelihood of selecting that cue to inform the production of action (e.g. Maddux et al., 2007; Holland & Maddux, 2010; Maddux & Holland, 2011a; 2011b). Thus, identifying the PPC as a locus for an α memory provides an opportunity for investigating the functional characteristics of such memories.

Chapter 3:

Secondary Visual Cortex and α_{Light} Expression

Introduction

The results of the previous chapter adhere to a role for PPC in storing α_{Light} memories. The transient pharmacological manipulations ostensibly interfered with the encoding, consolidation, and expression of α_{Light} memories that underlie performance in the serial prediction task. Specifically, infusions of NBQX into PPC prior to surprise phase sessions (experiment 1) or prior to test phase sessions (experiment 2) disrupted test phase performance, and the shift group advantage in learning about the light-food relation was eliminated by anisomycin infusions into PPC immediately, but not 24hrs, after surprise phase sessions (experiment 3). However, the diffusion of infusate into nearby secondary visual cortex (V2) could account for the patterns observed across those three experiments. Indeed, although weaker, we could have amended our original rationale to defensibly target V2 from the outset. Rodent visual cortex supplements collicular orienting to visual stimuli (Goodale and Carey, 1990; Zhao et al., 2014; Liang et al., 2015), and many effects attributed to the attentional modulation of primate visual cortex (Briggs et al., 2013; Gilbert & Li, 2013; Serences & Kastner, 2014) are both observable and inducible in rodent visual cortex (Goard & Dan, 2009; Niell & Stryker, 2010; Harris & Thiele, 2011; Lee et al., 2012; Bennett et al., 2013; Pinto et al., 2013; Polack et al., 2013; Fu et al., 2014; Lee et al., 2014; Reimer et al., 2014; Zhang et al., 2014; Vinck et al., 2015). The "Bucci buttress" that supported our PPC investigations extends feebly to V2: Bucci & MacLeod (2007) observed statistically unreliable hints of a surprise effect in a portion of V2, and Bucci et al. (1998) noted a slight depletion

of V2 cholinergic afferents attributable to immunotoxin diffusion from the PPC infusion sites.

In rat, PPC is anatomically distinct from caudal adjoining V2 (Kolb, 1990; Palomero-Gallagher & Zilles, 2015), but dissociations through causal analyses have not been reported. This is problematic as the two interconnected regions share many afferents and efferents (Miller & Vogt, 1984; Chandler et al., 1992; Reep et al., 1994; Wilber et al., 2014a; Bota et al., 2015) and may have overlapping functions (e.g. Torrealba & Valdes, 2008; Wilber et al., 2014b). Indeed, refined hodological and electrophysiological mapping of murine rodent visual cortex suggests that some visuotopic extrastriate subdivisions may straddle the architectonic borders of PPC and V2 (Krieg, 1946; Montero et al., 1973a; 1973b; Espinoza & Thomas, 1983; Zilles, 1985; Thomas & Espinoza, 1987; Malach, 1989; Coogan & Burkhalter, 1990; 1993; Montero, 1993; Palomero-Gallagher & Zilles, 2004; Swanson, 2004; Wang & Burkhalter, 2007; Garrett et al., 2014; Paxinos & Watson, 2014). In primates by contrast, distinguishing PPC from visual cortex is uncontroversial.

Any debate regarding primate PPC and visual cortex concerns descriptions of their interaction, say as *source* vs. *site* of attentional biases (c.f. Maunsell & Treue, 2006; Serences & Yantis, 2006; Bisley & Goldberg, 2010; Cisek & Kalaska, 2010; Gilbert & Li, 2013; Miller & Buschman, 2013; Cohen & Maunsell, 2014; Krauzlis et al., 2014). While *source* vs. *site* distinctions typically require qualification, considerable evidence supports the validity of the approach (Coull, 1998; Corbetta & Shulman, 2002; Petersen & Posner, 2012; Beck & Kastner, 2014; Nobre & Mesulam, 2014). Applying the framework here affords a testable prediction: if the analogous rat PPC is a source of visual attention bias signals (c.f.

Broussard, 2012), V2 may be a site to manifest that bias. That is, expression of α_{Light} may entail PPC modulations of V2 activity to subsequently amplify access of select visual representations into associative learning processes.

In this study, we probed the importance of V2 activity for the encoding and expression of α_{Light}, while also addressing diffusion to visual cortex as an account of the findings from our PPC study. To be exact, we used procedures identical to those in experiments 1 and 2, but delivered the infusates 1-1.5mm posterior, into V2. For comparison with experiment 1, experiment 4 investigated the importance of unperturbed V2 activity for the encoding of increased α_{Light} values through bilateral infusions of NBQX prior to both surprise phase sessions. For comparison with experiment 2, experiment 5 infused NBQX into V2 prior to each of the five test phase sessions to assess its role during the expression of increased α_{Light} values that had been encoded during the previous phase.

Methods

Subjects. A total of 80 male Long-Evans rats (Charles River Laboratories, Raleigh, NC) were used in this study: 32 in experiment 1 and 48 in experiment 2. Rats weighed 300-325 g upon arrival to the laboratory vivarium, and were given free access to food and water prior to surgery. Surgery was followed by 10-14 days of recovery before behavioral training. During the recovery period, the rats were handled daily. After recovery, they were food restricted to reach and subsequently maintain 85% of their free feeding weights throughout the course of the study. Rats were individually housed in a colony room with a 12:12 hr light-dark cycle. The care and experimental treatment of rats was conducted according to the

National Institutes of Health's *Guide for the Care and Use of Laboratory Animals*, and protocols were approved by the Johns Hopkins University Animal Care and Use Committee.

Apparatus. The behavioral training apparatus was the same as in Schiffino et al., (2014) and consisted of four separate chambers (22.9 X 20.3 X 20.3 cm). Each chamber had aluminum front and back walls, clear acrylic sides and top, and a floor of stainless steel rods (0.48 cm in diameter spaced 1.9 cm apart). A recessed food cup was located in the center of the front wall 2 cm above the floor, and was fitted with phototransistors to detect head entries. Two 45-mg sucrose pellets (Formula 5TUT, Test Diets, St. Louis, MO) delivered to the food cup served as the reinforcer. The light conditioned stimulus (CS) was generated by illumination of a 6-W panel lamp with a translucent covering, mounted 15 cm directly above the food cup. A 1500-Hz, 80-dB tone CS was presented via a speaker mounted on the inside wall of a sound-attenuating box that surrounded each chamber.

Surgery. Rats were anesthetized with 2-3% isoflurane mixed with oxygen and placed into the stereotaxic apparatus (Kopf Model 902, Tujunga, CA). After incision and craniotomy, four 1/8" self-tapping mounting screws were installed into the skull. Then, the dura was punctured with a 27-gauge needle and a 26-gauge guide cannula (PlasticsOne, Roanoke, VA), with stainless steel tubing cut to extend 3.5mm below the 8.0mm long pedestal, was implanted into each V2 at -5.3mm posterior and ±3.1mm lateral to bregma, to a depth of 0.9 mm below the skull surface. These coordinates differed only along the rostrocaudal axis from those used for PPC cannulations in experiments 1-3 (Schiffino et al., 2014). Cannulae were held in place with dental acrylic and fitted with obturators that were cut to match the length of the guide. Once the acrylic set, the incision was closed with surgical staples and topical antibiotic ointment was applied to the wound edges. Then, all rats

received subcutaneous 0.02 mg/kg injections of sterile buprenorphine HCl (Sigma, St. Louis, MO) to ameliorate pain.

Behavioral training procedures. Table 1 provides an outline of the behavioral training procedures. Hungry rats were first given 10 sucrose pellets in their home cages to familiarize them with the reinforcer. Each training session in each phase of the experiments included 16 trials, distributed across random intertrial intervals, which averaged 4 min (range = 2 to 6 min). The rats were first trained to eat sucrose pellets from the recessed food cups in a single session, which included 16 unsignaled reinforcer deliveries. Then, to establish a strong light-tone association during the expectancy phase, all rats received trials consisting of a 10-s light → 10-s tone serial compound. In each session of this phase, half of the 16 trials had the light→tone compound reinforced with sucrose pellets and the other half were non-reinforced. Trial order in each session was randomly determined. After 15 sessions of expectancy training, rats were allocated into performance-matched shift and consistent groups, and given 2 surprise phase sessions. During each surprise session, light→tone prediction error was induced for the shift rats by omitting the tone on the 8 nonreinforced trials, while consistent rats had their light→tone expectancies confirmed through continuation of the expectancy protocol. Finally, in each of the 5 sessions in the test phase, all rats received 16 presentations of the light CS alone followed immediately by sucrose pellet reinforcement. Greater acquisition of food-cup responses to the light CS was taken as evidence of relatively greater α_{Light} values.

Behavioral measure and analysis. The response measure was the percentage of time spent in the food cup, as assessed by interruption of the infrared photobeam. Trial epochs

were defined as a 5 s stimulus-free pre-CS period (immediately prior to the light CS), the first 5 s of the light CS, the second 5 s of the light CS, the first 5 s of the tone CS, the last 5 s of the tone CS, and the 5 s initiated by reinforcer delivery. Conditioned food cup responding was assessed during the latter half of CS presentations because in that epoch, food cup CRs are more frequent and less contaminated by conditioned orienting behaviors (Holland, 1977).

Responding during the pre-CS, light, and tone (when applicable) epochs were each analyzed with separate ANOVAs with treatment (shift or consistent), and drug infusion (NBQX or saline) as between-subject variables, and repeated measures on the within-subjects variable of session blocks. The Greenhouse-Geisser procedure was used to correct for violations of sphericity. In the test phase, the ANOVAs were followed by planned contrasts to evaluate the hypotheses that behavioral condition groups differed within each drug treatment (shift-vehicle vs. consistent-vehicle; shift-NBQX vs. consistent-NBQX) and that drug treatment groups differed within each behavioral condition (shift-vehicle vs. shift-NBQX; consistent-vehicle vs. consistent-NBQX).

Drugs and infusion procedures. The procedures for experiments 4 and 5 were identical to those used in experiments 1 and 2, respectively. In both experiments, rats had their obturators removed and reinserted before each of the expectancy sessions to familiarize them with manipulation of their cannula headsets. Two 33-gauge injector cannulae that extended 0.4mm below the tip of the guide were connected by PE50 tubing to separate 10-μL Hamilton syringes in a multiple-syringe pump (KD Scientific, Holliston, MA). The pump simultaneously administered 0.5 μL of infusate bilaterally into V2, over one minute. After infusion, the injector was left in place for an additional minute. After removal of the

injectors, the obturators were reinserted. In both experiments, V2 activity was perturbed by NBQX. NBQX (Sigma) was dissolved at a concentration of 20 μg/μL in 0.1M PBS vehicle. Infusions of NBQX were delivered within 20 minutes prior to the onset of each surprise session (experiment 4) or each test session (experiment 5). Vehicle rats in each behavioral condition received infusions of PBS.

Histological procedures. After completion of behavioral testing, the rats were deeply anesthetized with isoflurane and perfused intracardially with 0.9% saline followed by 3.7% formalin solution. Once fixed, brains were removed and stored at 4°C in 3.7% formalin 12% sucrose solution. Brains were sliced on a freezing microtome and 40-μm coronal sections were taken in series. To confirm cannula tip placements in the bilateral V2, every third section was mounted on glass slides, dehydrated in ascending concentrations of alcohol, defatted in xylene, and stained with thionin. Slides were coverslipped using Permount thinned with xylene, and examined with a light microscope.

Results

Histological results. Of the 80 rats acquired for the study, the data from 6 were excluded. In experiment 4, one of the 32 rats was excluded because its headset detached. In experiment 5, 4 of the 48 rats were excluded after their headsets detached, and one rat was excluded for missed cannula placement. Assessments of cannula tip placements confirmed that V2 was the site of injection for all rats whose data were included for further analysis (Figure 3). In experiment 4, the final numbers of rats in the shift-NBQX, shift-vehicle, consistent-NBQX, and consistent-vehicle conditions were 8, 8, 8, and 7, respectively. In experiment 5, those sample sizes were 11, 10, 10, and 12, respectively.

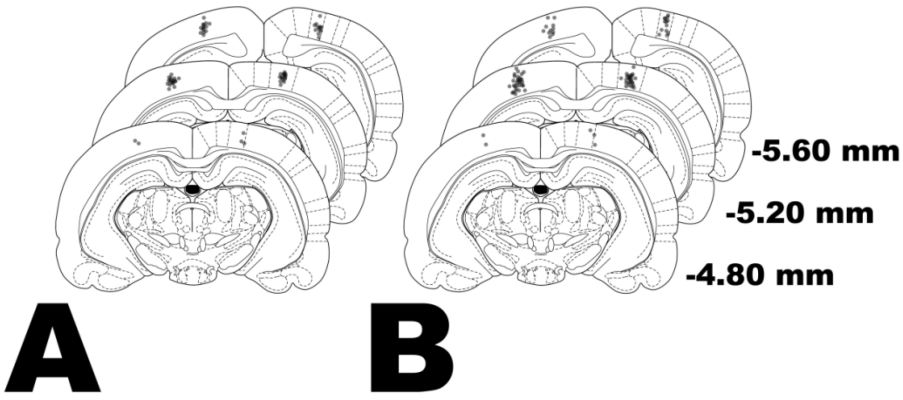


Figure 3. Schematic Representation of Injector Cannula Tip Placements for Rats Included in Experiment 4(A), Experiment 5(B).

The numbers on the right indicate distance (mm) from bregma along the rostrocaudal axis. For each placement, a single black dot of 50% opacity was drawn using Adobe Photoshop. Thus, darker areas indicate greater overlap.

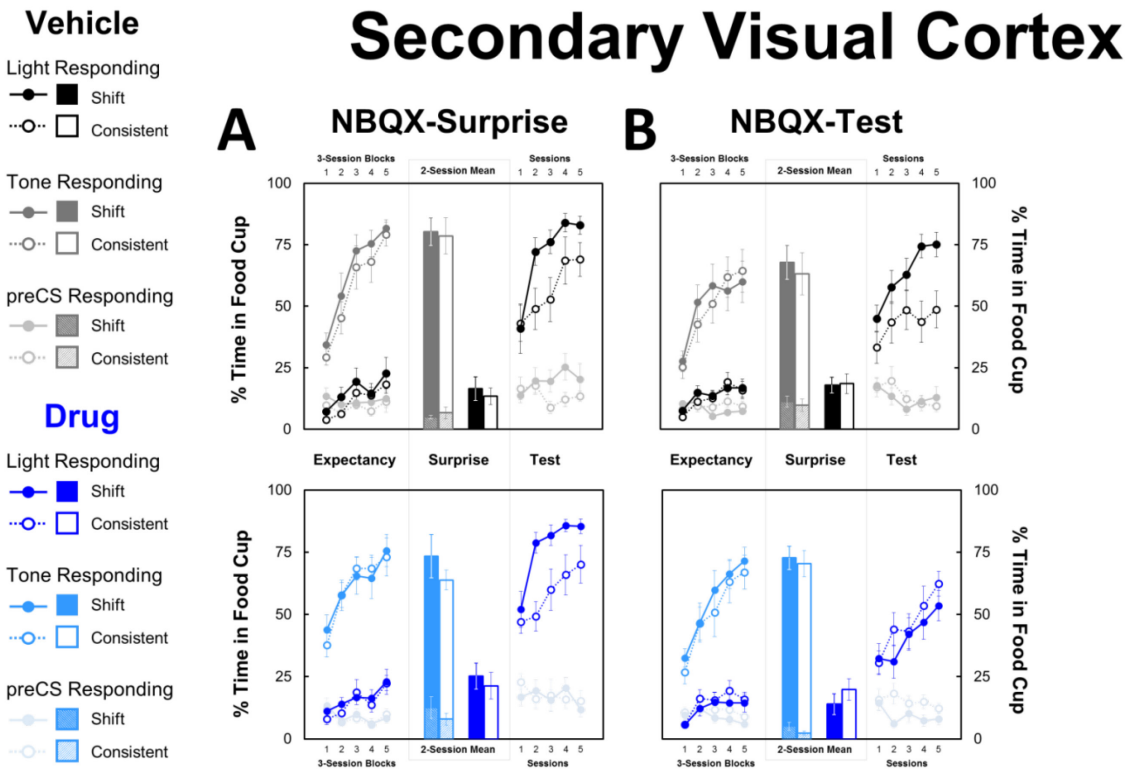


Figure 4. Conditioned Food Cup Responding for Experiments 4-5

Mean (± SEM) food-cup responding during pre-CS, light, and tone measurement epochs sequentially across all three phases (expectancy, surprise, and test) of experiment 4 (panel 4A) and experiment 5 (panel 4B). See the legend for epoch and group (drug treatment x behavioral condition) designations, and see text for statistical results. Rats received infusions of vehicle (grayscale; top) or NBQX (shades of blue; bottom) into SVC prior to both surprise phase sessions in experiment 4 (4A), or before each test phase session in experiment 5 (4B). Analysis of expectancy and surprise phase data did not reveal major caveats: rats acquired and maintained comparably high levels of food-cup responding to the tone while exhibiting minimal conditioning to the light. The right side of each panel depicts the acquisition of food-cup responding over the course of the five test phase sessions. The shift group advantage in test phase learning was robust to surprise phase perturbations of SVC activity. However, SVC function during the test phase appears critical for shift animals to exhibit benefits induced by surprise in the previous phase.

Behavioral results. Figure 4 depicts food-cup responding during pre-CS, light, and tone measurement epochs sequentially across all three phases (expectancy, surprise, and test) of experiment 4 (panel 4A) and experiment 5 (panel 4B).

Expectancy phase. In each Fig. 4 panel, the leftmost portion shows that within each of the two experiments, all groups of rats acquired comparably high levels of food-cup responding to the tone while exhibiting minimal conditioning to the light. For both experiments, the results of separate behavioral condition (shift vs. consistent) x drug treatment (NBQX vs. vehicle) x three-session block (1-5) ANOVAs on responding during each measurement epoch (pre-CS, light, and tone) confirmed this assertion. Importantly, no evidence of a significant behavioral condition x drug treatment interaction was observed for any of the three epochs in either experiment (*P*s > .490), nor did those interactions change across blocks (*P*s > .426). The pervasive effects of block (*P*s < .040) were never accompanied by main effects of behavioral condition (*P*s > .214) or drug treatment (*P*s > .341). In experiment 4, animals to be infused with NBQX initially demonstrated greater responding to the tone, but that difference disappeared by the third block (drug treatment x block interaction: $\varepsilon = 0.63$, $F_{4, 108} = 3.58$, $P = .024$). In experiment 5, pre-CS responding slightly diverged between behavioral conditions over the last three blocks (behavioral condition x block interaction: $\varepsilon = 0.83$, $F_{4,156} = 2.66$, $P = .045$), whereby pre-CS responding by shift allocated animals decreased while responding by consistent allocated animals went unchanged. No other interactions with block were significant (*P*s > .378), and the negligible differences in tone and pre-CS responding described above were unlikely to affect the outcome of this study. Indeed, ANOVAs on means from the last two sessions of the expectancy phase did not find significant interactions (*P*s > .560) or effects (*P*s > .314) on

responding in any epoch for either experiment. Thus, all groups of rats within each experiment exhibited comparable behavior before we initiated the surprise phase.

Surprise phase. The bars in Fig. 4 depict food-cup response means collapsed across the two surprise phase sessions. For both experiments, data from each of the three measurement epochs were subjected to behavioral condition x drug treatment ANOVAs. In experiment 4, some rats from both behavioral conditions received infusions of NBQX prior to each session, whereas the remaining rats received infusions of vehicle. Importantly, there were no significant effects of drug treatment on pre-CS responding ($F_{1, 27} = .091$, $P = .765$), responding during the light ($F_{1, 27} = 1.57$, $P = .221$), or responding during the tone ($F_{1, 27} = 2.93$, $P = .098$). There were no effects of behavioral condition (*P*s >.520), and the behavioral condition x drug treatment interaction was not significant for any measure (*P*s >.884). In experiment 5, rats did not receive infusions of NBQX or vehicle until the test phase, but data from the surprise sessions were analyzed with subsequent drug treatment included as a factor. No effects of subsequent drug treatment (*P*s > .454) or behavioral condition (*P*s > .408) were significant for responding during either cue, nor did those variables interact (*P*s > .502). Thus, for both experiments, rats in all groups began the test phase after showing similar levels of responding to both the light and tone during the surprise phase.

Test phase. The rightmost portion of each Fig. 4 panel shows the primary data of this study, the acquisition of food-cup responding to the light during the test phase. Mixed, repeated-measures ANOVAs on light and pre-CS responding consisted of the between-subjects variables of behavioral condition and drug treatment, and the within-subjects variable of test sessions (1–5) with Greenhouse–Geisser correction.

In experiment 4 (Fig. 4A), rats in the shift condition acquired greater food-cup responding to the light than rats in the consistent condition regardless of whether NBQX or vehicle was infused prior to surprise phase sessions. No significant effect or interactions involving drug treatment were observed (*P*s > .443), while the significant effect of behavioral condition ($F_{1, 27} = 11.74$, $P = .002$) interacted with session ($\varepsilon = 0.42$, $F_{4, 108} = 3.81$, $P = .036$). Indeed, planned contrasts confirmed that the greater test responding to the light for either shift group relative to their infusate-matched consistent groups was reliable for both vehicle ($P = .043$) and NBQX treatments ($P = .011$), while drug treatment groups did not differ reliably within either behavioral condition (*P*s > .416).

By contrast, in experiment 5 (Fig. 4B), infusions of NBQX prior to each test phase session eliminated the shift condition advantage in learning about the light. The marginal behavioral condition x drug treatment interaction ($F_{1, 39} = 3.91$, $P = .055$) was qualified significantly by session ($\varepsilon = 0.80$, $F_{4, 156} = 4.63$, $P = .003$). Furthermore, vehicle-infused rats in the shift condition showed significantly greater responding than either vehicle-infused rats in the consistent condition ($P = .034$) or NBQX-infused rats in the shift condition ($P = .020$). No difference was observed between infusion groups in the consistent condition ($P = .721$) or between behavioral groups that were infused with NBQX ($P = .542$).

Analyses of pre-CS responding in the test phase did not reveal caveats. In experiment 4, ANOVAs did not find any reliable effects (*P*s > .381) or interactions (*P*s > .119). In experiment 5, the significant effect of session ($\varepsilon = 0.82$, $F_{4, 156} = 5.11$, $P = .002$) interacted with behavioral condition ($\varepsilon = 0.82$, $F_{4, 156} = 2.70$, $P = .044$), but no other effects (*P*s > .204) or interactions were significant (*P*s > .301). Importantly, the shift advantage for

vehicle-infused rats was not obscured by the elevated levels of pre-CS responding observed in the consistent condition.

Discussion

The results of the current study complement those of the previous chapter by dissociating the importance of PPC and V2 during the encoding of surprise-increased α_{Light} values. In experiment 1, surprise-phase infusions of NBQX into PPC severely disrupted test phase performance of the shift group rats. In experiment 4, surprise-phase infusions of NBQX into V2, 1-1.5mm posterior to the PPC infusion sites, did not have any observable effects on light-food learning. By contrast, test-phase infusions of NBQX into PPC (experiment 2) or V2 (experiment 5) eliminated the shift group advantage in light-food learning. Importantly, NBQX infusions into V2 prior to test phase sessions did not affect learning in the consistent group, so perturbations of V2 activity did not preclude the formation of light-food associations that underlie conditioned approach. Since rostral striate cortex (V1) corresponds retinotopographically to the lower portions of the visual field (Espinoza & Thomas, 1983; Montero, 1993), it is unlikely that diffusion of NBQX to V1 contributed significantly in any experiment. Furthermore, given the functional dissociation of PPC and V2 during the surprise phase (experiment 1 vs. experiment 4), we reject the notion that diffusion of NBQX between PPC and V2 injections sites suffices to account for our observations. Instead, we find it more likely that intact functioning of PPC, but not V2, is required for α_{Light} values to increase following surprising tone omissions, while functioning of both areas is necessary during the test phase for increased α_{Light} values to facilitate learning about the light.

In PH, to reconcile $\alpha_{stimulus}$ values with experience, computational networks generate a prediction given registry of a stimulus, determine the inaccuracy of that prediction, then adjust $\alpha_{stimulus}$ accordingly to bias attention towards future opportunities for learning (c.f. Grossberg & Versace, 2008). Here, following Phase 1 training, the light stimulus prompts anticipation of the tone. Then, during the surprise phase, PH networks must (1) register the light, (2) retrieve an expectation about the occurrence of the tone, (3) assess the extent of divergence between that expectation of tone and reality, i.e. compute prediction error or surprise, (4) use that surprise computation to adjust α_{Light} values, and (5) archive updated α_{Light} in memory. It is quite plausible that a network involving PPC performs each of those steps (see Chapter 2). Moreover, considering the applicability of canonical organization schemes to rodent cortical vision (Malach, 1989; Montero, 1993; Wang & Burkhalter, 2007; 2013; Huberman & Niell 2011; Wang et al., 2011; 2012; Glickfeld et al. 2013, 2014; Vermaercke et al., 2014; Cooke & Bear, 2015; Laramee & Boire, 2015; Niell, 2015), V2 extraction of stimulus features (e.g. Montero & Jian, 1995; Andermann et al., 2011; Marshel et al., 2011) and subsequent relay to PPC may be an idiosyncratic necessity during α_{visual} parameter encoding. However, when that stimulus alters the luminance of the entire visual field, as in experiment 5, intact V2 function, and therefore V2 input to PPC, appears surplus to requirements (see Dean, 1981; 1990). Presumably, during the encoding of surprise-altered α_{Light} memories in experiment 5, PPC received the majority of its requisite visual information from superior colliculus (SC) by way of thalamic LP (Linden and Perry, 1983; Sugita et al., 1983; Dean & Redgrave, 1984, Dreher et al., 1985; Chandler et al., 1992; Lane et al., 1993; Reep et al., 1994; Bucci et al., 1999; Tohmi et al., 2014; Nakamura et al., 2015; Sefton et al., 2015), with V1 supplying parallel or supplementary input (Hughes, 1977; Scheff & Wright,

1977; Takahasi, 1985; Reep et al., 1994; Bourassa & Deschenes, 1995; Masterson et al., 2009; Sherman & Guillery, 2011; Sherman, 2012; Bota et al., 2015).

Circuit components and mechanisms of a_{Light} expression

The expression of α_{Light} is likely mediated by a cortico-basal ganglia rat attention network (Corwin & Reep, 1998; Reep & Corwin, 2009) analogous to that of primates (Baluch & Itti, 2011; Petersen & Posner, 2012; Miller & Buschman, 2013; Clark et al., 2015). In addition to PPC and V2 (and cholinergic SI/nBm), reasonable candidate constituents of the rat network include their hodological partners in PFC, V1, thalamic nuclei, SC, and striatal subregions, each of which have been implicated in orienting and visuospatial attention in murine rodents. Specifically, PPC and V2 both reciprocate connections with V1, AGm and thalamic LP (Miller & Vogt, 1984; Takahashi, 1985; Reep et al., 1994; Burwell & Amaral, 1998; Kamishina et al., 2009; Agster & Burwell, 2009; Bota et al., 2015), and provide collateralized input to thalamic reticular nucleus (TRN) (Coleman & Mitrofanis, 1996; Vertes et al., 2015). Contained within AGm is a candidate analog of primate frontal eye field (FEF) (Crowne, 1983; Squire et al., 2013) termed the rat frontal orienting field (FOF), which coordinates eye, head, and vibrissae movements to induce overt shifts of attention (Kanki et al., 1983; Sinnamon and Galer, 1984; Crowne et al., 1986; Neafsey, et al., 1986; Erlich et al., 2011; 2015; Hanks et al., 2015). Although the role of thalamic LP in rodent attention remains largely uncharacterized, the putative homolog in primate, pulvinar, as well as the adjacent TRN are integral components of attention networks (Reep & Corwin, 2009; Saalmann & Kastner, 2011). The prevailing view of TRN function continues to be the implementation of an attentional spotlight (Crick, 1984), and evidence suggests that such a

role for TRN may extend to rats (Montero 1997; Weese et al., 1999; McAlonan et al., 2000; Montero, 2000; Yu et al., 2009; Petrof & Brown, 2010).

PPC and V2 gain extrathalamic access to subcortical loops through efferents to medial SC and overlapping regions of dorsal striatum (DS) (McGeorge & Faull, 1989; Harvey & Worthington, 1990; McHaffie et al., 2005; Comoli et al., 2012; Dudman & Gerfen, 2015). Fundamental functions of rodent SC during visual orienting (Goodale & Murison, 1975; Goodale et al., 1978; Dean & Redgrave, 1984; Zhao et al., 2014; Ngan et al., 2015) are comparable to those of primates (Krauzlis et al., 2013; Corneil & Munoz, 2014) and avian optic tectum (e.g. Mysore & Knudsen, 2012; 2013; 2014). While rodent DS or its primate homolog are not typically ascribed functions in attention (Balleine, 2005; Balleine & O'Doherty, 2010; Gruber & McDonald, 2012; but see Hikosaka et al., 2000; Yamamoto et al., 2012; Seger, 2013; Anderson et al., 2014), mounting evidence suggests that subregions of rat DS are involved in visual orienting and shifts of attention (Han et al., 1997; Van Vleet et al., 2000; Rogers et al., 2001; Christakou et al., 2001; 2005; Chudasama & Robbins, 2006; Agnoli & Carli, 2011; Aoki et al., 2015), including that which occurs in the serial prediction task (Asem et al., 2015; Esber et al., 2015). It seems likely that each of those rat papers affected a hub for directed attention termed dorsocentral striatum (DCS), which receives converging inputs from PPC, V2, AGm, and LP (Reep et al., 2003; Cheatwood et al., 2003; 2005; Kamishina et al., 2008; Reep & Corwin, 2009; c.f. Jarbo and Verstynen; 2015). Additionally, both PPC and V2 densely innervate posterior aspects of dorsomedial striatum (pDMS). Through those projections, PPC-V2 might expedite the formation of light-food associations mediated by pDMS activity (c.f. Corbit & Janak, 2010; Reig & Silberberg, 2014). Perhaps those cortical efferents interact with those from thalamic parafasicular nucleus (PF)

to regulate cholinergic interneurons (Matsumoto et al 2001; Minamimoto & Kimura, 2002; Brown et al., 2010; English et al., 2011; Bradfield et al., 2013).

Neurobiological sources of attentional control, including PPC, broadcast signals to bias access of representations to other limited-capacity processes (Posner & Peterson, 1990; Coull, 1998; Serences & Yantis, 2006; Bisley & Goldberg, 2010; Gottlieb, 2014; Nobre & Mesulam, 2014). Frequently, that bias is achieved through feedback modulation of activity in sensory areas like visual cortex since alterations to the relative strength, clarity, or vividness of sensorial representations affect their proclivity for processing (c.f. Titchener, 1908; Poort et al., 2015; Zold & Shuler, 2015; Cooke & Bear, 2015). It is therefore plausible that rat PPC modulates activity in visual cortex to influence a subset of the systems engaged by light-food conditioning, including those underlying conditioned approach, as a means by which α_{Light} values manifest to facilitate learning.

Chapter 4:

Amygdala Central Nucleus and α_{Light} Consolidation

Introduction

The results reported strengthen the notion that PPC contributes essential components to the storage of α_{Light} information. Perturbations to PPC activity during the encoding (experiment 1) and expression (experiment 2) of surprise-altered α_{Light} memories impaired performance in the serial prediction task, while NBQX infusions into V2 affected the expression (experiment 5), but not the encoding (experiment 4) of those memories. Importantly, infusions of anisomycin into PPC immediately, but not 24hrs, after surprise phase sessions interfered with the consolidation of increased α_{Light} memories (experiment 3). This consolidation process likely relies upon interactions between multiple brain regions, and since CeA activity during encoding matters (Holland & Gallagher, 2006), it is reasonable to consider a role for this nucleus. For example, it may be that the consolidation of surprise-phase encoded α_{Light} memories involves protracted interactions of CeA with diffuse neuromodulatory systems that include dopaminergic SNcl, cholinergic SI/nBm, and orexigenic hypothalamus (see Holland & Gallagher, 2006; Holland & Maddux, 2010; Wheeler et al., 2014).

Across species, the amygdala modulates consolidation of different types of memory through interactions with multiple neuroanatomical and biochemical systems (Cahill & McGaugh, 1998; McGaugh et al., 2002; Roozendaal et al., 2009; McGaugh & Roozendaal, 2009; Roozendaal & McGaugh, 2011; McIntyre et al., 2012). In the rat, extensive research

using myriad appetitive or aversive behavioral preparations has characterized basolateral complex (BLA) contributions to the stabilization of memories about motivationally significant experiences (Schafe et al., 2001; Pare, 2003; McGaugh, 2004; Huff et al., 2013; Hermans et al., 2014). Considering other attributes of BLA function, it seems likely that those memories represent specific sensory properties of the motivationally significant event (c.f. Holland & Gallagher, 1999, Gallagher & Schoenbaum, 1999; Everitt et al., 2000; 2003; Balleine & Killcross, 2006; Seymour & Dolan, 2008; Clark et al., 2012). However, α_{Light} is a parameter for the control of visuospatial attention, not an associative memory imbued with motivational significance. It is notable therefore that performance in the serial prediction task is unaffected by BLA neurotoxic lesion (Holland et al., 2001, but see Herry et al., 2007; Roesch et al., 2010; Chang et al., 2012; Esber et al., 2012; Boll et al., 2013; Esber & Holland, 2014).

In the three experiments of this chapter, we examined the importance of CeA function for the consolidation of α_{Light} memories through post-surprise session infusions into the nucleus. In experiment 6, anisomycin was infused bilaterally to inhibit translation. In experiment 7, lidocaine was infused bilaterally to suppress conduction down CeA axons. The rationale for selecting lidocaine (see Discussion for details) emerged from reports that intra-amygdalar pretreatment of the anesthetic attenuated subsequent amnesia while concomitantly preventing an inordinate release of monoamines that was secondary to intra-amygdalar anisomycin (Canal et al., 2007; Sadowski et al., 2011). In experiment 8, fluorescent muscimol (FCM) was infused bilaterally to achieve greater specificity than lidocaine by sparing conductance down fibers of passage, and an addendum experiment assessed the spread of FCM at various post-infusion intervals.

Methods

Subjects. Male Long-Evans rats (Charles River Laboratories, Raleigh, NC) were used in this study: 96 in experiment 6, 48 in experiment 7, and 64 in experiment 8. Rats weighed 300-325 g upon arrival to the laboratory vivarium, and were given about a week of free access to food and water prior to surgery. Surgery was followed by 10-14 days of recovery before behavioral training. During the recovery period, the rats were handled for at least 2 min each day. After recovery, they were food restricted to reach and subsequently maintain 85% of their free feeding weights throughout the course of the study. Rats were individually housed in a colony room with a 12:12 hr light-dark cycle. The care and experimental treatment of rats was conducted according to the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals*, and protocols were approved by the Johns Hopkins University Animal Care and Use Committee.

Apparatus. The behavioral training apparatus consisted of four separate chambers (22.9 X 20.3 X 20.3 cm). Each chamber had aluminum front and back walls, clear acrylic sides and top, and a floor of stainless steel rods (0.48 cm in diameter spaced 1.9 cm apart). A recessed food cup was located in the center of the front wall 2 cm above the floor, and was fitted with phototransistors to detect head entries. Two 45-mg sucrose pellets (Formula 5TUT, Test Diets, St. Louis, MO) delivered to the food cup served as the reinforcer. The light conditioned stimulus (CS) was generated by illumination of a 6-W panel lamp with a translucent covering, mounted 15 cm directly above the food cup. A 1500-Hz, 80-dB tone CS was presented via a speaker mounted on the inside wall of a sound-attenuating box that surrounded each chamber.

Surgery. Rats were anesthetized with 2-3% isoflurane mixed with oxygen and placed

into the stereotaxic apparatus (Kopf Model 902, Tujunga, CA). After incision and craniotomy, four 1/8" self-tapping mounting screws were installed into the skull. Then, the dura was punctured with a 27-gauge needle and 26-gauge guide cannulae (PlasticsOne, Roanoke, VA), with stainless steel tubing cut to extend 8.5mm below the 8.0mm long pedestal, were implanted dorsal to each CeA at -2.4mm posterior and ±4.3mm lateral to bregma, to a depth of 5.9 mm below the skull surface. Cannulae were held in place with dental acrylic and fitted with obturators that were cut to match the length of the guide. Once the acrylic set, the incision was closed with surgical staples and topical antibiotic ointment was applied to the wound edges. Then, all rats received subcutaneous 0.02 mg/kg injections of sterile buprenorphine HCl (Sigma, St. Louis, MO) to ameliorate pain.

Behavioral training procedures. Table 1 provides an outline of the behavioral training procedures. Hungry rats were first given 10 sucrose pellets in their home cages to familiarize them with the reinforcer. Each training session in each phase of the experiments included 16 trials, distributed across random intertrial intervals, which averaged 4 min (range = 2 to 6 min). The rats were first trained to eat sucrose pellets from the recessed food cups in a single session, which included 16 unsignaled reinforcer deliveries. Then, to establish a strong light-tone association during the expectancy phase, all rats received trials consisting of a 10-s light → 10-s tone serial compound. In each session of this phase, half of the 16 trials had the light→tone compound reinforced with sucrose pellets and the other half were non-reinforced. Trial order in each session was randomly determined. After 10 sessions of expectancy training, rats were allocated into performance-matched shift and consistent groups, and given 2 surprise phase sessions. During each surprise session, light→tone

prediction error was induced for the shift rats by omitting the tone on the 8 nonreinforced trials, while consistent rats had their light→tone expectancies confirmed through continuation of the expectancy protocol. Finally, in each of the 5 sessions in the test phase, all rats received 16 presentations of the light CS alone followed immediately by sucrose pellet reinforcement. Greater acquisition of food-cup responses to the light CS was taken as evidence of relatively greater α_{Light} values.

Behavioral measure and analysis. The response measure was the percentage of time spent in the food cup, as assessed by interruption of the infrared photobeam. Trial epochs were defined as a 5 s stimulus-free pre-CS period (immediately prior to the light CS), the first 5 s of the light CS, the second 5 s of the light CS, the first 5 s of the tone CS, the last 5 s of the tone CS, and the 5 s initiated by reinforcer delivery. Conditioned food cup responding was assessed during the latter half of CS presentations because in that epoch, food cup CRs are more frequent and less contaminated by conditioned orienting behaviors (Holland, 1977).

Responding during the pre-CS, light, and tone (when applicable) epochs were each analyzed with separate ANOVAs with behavioral condition (shift or consistent) and drug treatment (immediate or delayed: anisomycin in experiment 6; lidocaine in experiment 7; FCM in experiment 8) as between-subject variables, and repeated measures on the within-subjects variable of session blocks (1-5). The Greenhouse-Geisser procedure was used to correct for violations of sphericity. The ANOVAs on test phase data were supplemented by planned contrasts to evaluate the hypotheses that behavioral condition groups differed within each drug treatment (shift-immediate vs. consistent-immediate; shift-delayed vs.

consistent-delayed) and that drug treatment groups differed within each behavioral condition (shift-immediate vs. shift-delayed; consistent-immediate vs. consistent-delayed).

Drugs and infusion procedures. In experiment 6, anisomycin was infused to inhibit translation in CeA. Anisomycin (Sigma) was dissolved into HCl at a concentration of 125 μg/μL in 0.9% saline vehicle and the pH was adjusted to 7.2 (Nader et al., 2000). Notably, the concentration of anisomycin in this infusate was twofold greater than that delivered into PPC in experiment 3. In experiment 7, 2% lidocaine hydrochloride solution (Vedco) was infused to disrupt the propagation of action potentials down CeA axons. In experiment 8, the GABA-$_A$ agonist muscimol (Beaumont et al., 1978) conjugated to the BODIPY® TMR-X fluorophore through covalent amide bonding (Molecular Probes) was infused to reversibly inactivate CeA neurons while minimizing perturbation of transmission down fibers of passage. The FCM fluorophore has excitation and emission peaks at 543 and 572 nm, respectively, and is highly lipophilic (Allen et al., 2008). FCM was dissolved into 0.9% saline vehicle at a concentration of 0.5 μg/μL. In each experiment, rats had their obturators removed and reinserted after each of the expectancy sessions, to familiarize them with manipulation of their headstages. Two 33-gauge injector cannulae (0.2mm O.D., 0.1mm I.D.) that extended 2.0mm below the tip of the guide were connected by PE50 tubing to separate 10-μL Hamilton syringes in a multiple-syringe pump (KD Scientific, Holliston, MA). In experiments 6 and 7, the pump simultaneously administered 0.2 μL of infusate over one minute. In experiment 8, 0.5 μL of infusate was delivered over two minutes. A pilot fear conditioning experiment found the volume of FCM used for experiment 8 to be sufficient to disrupt the expression of freezing behavior following infusion into bilateral CeA, while 0.2 μL infusions were considerably less effective. After infusion, the injector was left in place for

an additional minute. After removal of the injectors, the obturators were reinserted. Rats in the "immediate" drug treatment received infusions of anisomycin (experiment 6), lidocaine (experiment 7), or FCM (experiment 8) immediately after the end of each surprise session, whereas rats in the "delayed" condition received saline-only infusions at these times. The delayed rats also received anisomycin, lidocaine, or FCM infusions, but at 24 h after each surprise session. Rats in the immediate condition received saline-only infusions at these (24-hr delay) times. Thus, each rat received two anisomycin (experiment 6), lidocaine (experiment 7), or FCM (experiment 8) infusions and two saline infusions in the surprise phase, but only the rats in the immediate drug treatment received the anisomycin, lidocaine, or FCM at a time when it was likely to interfere with CeA-dependent consolidation of memories acquired during the surprise sessions.

Histological procedures. All rats except for those allocated to the supplemental FCM spread study (n = 29 from experiment 8) were deeply anesthetized and perfused intracardially with 0.9% saline followed by 3.7% formalin solution after completion of behavioral testing. After removal of the headstage, brains were removed and stored at 4°C in 3.7% formalin 12% sucrose solution. These brains were sliced on a freezing microtome and 40-μm coronal sections were taken in series. To confirm cannula tip placements in the bilateral CeA, every third section was mounted on glass slides, dehydrated in ascending concentrations of alcohol, defatted in xylene, and stained with thionin. Slides were coverslipped using Permount thinned with xylene, and examined with a light microscope.

Time-course assessment of FCM spread. A total of 29 rats were used for this study, 8 of which were sacrificed during the surprise phase, while the remaining 21 rats received an additional FCM infusion after completion of behavioral testing. The surprise phase rats (n = 8) were sacrificed to garner preliminary estimates of spread under conditions that approximated those from animals whose behavior was eventually tested, i.e. first (n =4) or second (n =4) FCM infusion in food-restricted rats. In that preliminary assessment, single samples were taken for each of 8 post-infusion timepoints (hrs): 0.25, 0.5, 1, 2, 4, 8, 24, 48. For each FCM infusion group (first or second), one rat provided the estimate for 0.25 hrs and 0.5 hrs, another for 1 hr and 2 hrs, another for 4 hrs and 8 hrs, and the last for 24hrs and 48hrs. In the first infusion group, all rats received a unilateral dose of FCM immediately after the end of the first surprise session. The contralateral dose was administered fifteen minutes later for the first rat, an hour later for the second rat, four hours later for the third rat, and 24hrs later for the last rat. Rats were then euthanized at the appropriate time. In the second infusion group, all four rats received a bilateral dose of FCM immediately after the first surprise session, bilateral infusions of vehicle 24 hrs later (during their day off from the behavioral procedure), and a second staggered FCM dose, in the same manner described for the first infusion group, after the second surprise session (24 hrs after the vehicle dose). The remaining 21 rats were given *ad lib* access to food and water after their last test session. The results of the preliminary surprise phase assessment suggested that from 2 hrs onwards, substantial FCM was not detectable outside of the injector track proximity. Additionally, in two samples of the earlier timepoints (0.25 and 0.5hrs), the injector tips failed to breach the bundle of myelinated fibers overlying CeA. Thus, the 21 rats (3 rats per timepoint) were used for analysis of 7 post-infusion timepoints (mins): 0, 15, 30, 45, 60, 90, 120. Bilateral FCM

doses were administered simultaneously, and rats were then euthanized at the appropriate time. We describe observations from the latter, more precise timecourse below.

Thirty seconds prior to each timepoint, rats were deeply anesthetized with isoflurane and decapitated shortly thereafter. Their brains were quickly removed (~1 min) then placed on a small plastic tray that had been buried in crushed dry ice. Brains were then frozen with crushed dry ice gradually to mitigate warping (~2 mins) before the tray and brain were wrapped with cold aluminum foil and stored at -70°C until slicing. Brains were thawed in a cryostat (-15°C) and coronal sections of 60 μm thickness were cut in series. Sections spanning from the level of bregma to ~4 mm posterior were mounted directly from the blade onto glass slides, which were then placed into a dark box and stored at 4°C.

Dispersion of FCM was visualized with a Zeiss AxioZoom.V16 microscope equipped with a HXP200C metal halide lamp and Filterset 43HE (Carl Zeiss, Thornwood, NY). The 43HE filter (excitation BP 550/25; emission BP 605/70) is compatible with BODIPY® TMR-X excitation and emission spectra (Zeiss), although peak emission is not transmitted. To capture images, Zeiss Zen Blue 2012 software controlled acquisition by a mounted Hamamatsu ORCA-Flash4.0 V2 digital camera. Slices were surveyed for the presence of fluorescence and compared against darkfield illumination during initial assessments. Afterwards, to increase resolution of anatomical landmarks, a droplet of Fluoromount (Electron Microscopy Sciences) was applied to a given slice that was then coverslipped. Since application of mounting medium causes FCM to diffuse, images were captured with expediency. These pictures were compared against their corresponding dry tissue images to confirm that spurious spread was minimal.

Results

Histological results. Of the 144 rats acquired for the study, the data from 43 were excluded. In experiment 6, three of the 96 rats were excluded because their headstages detached, three rats were removed due to infectious brain lesion, one ataxic rat was sacrificed, six rats were excluded for missed cannula placement, and one rat died during surgery. Notably, in 17 additional rats, neurotoxic lesions of CeA were observed, so those rats were excluded (c.f. Morris et al., 2006). In experiment 7, four of the 48 rats were excluded after their headstages detached, four rats were excluded for missed cannula placement, and one rat died during surgery. In experiment 8, 8 of the 64 rats were sacrificed during the surprise phase as part of the supplemental spread study, two rats were sacrificed after their headstages detached, and four rats were excluded for missed cannula placement. Assessments of cannula tip placements confirmed the site of injection for all rats whose data were included for behavioral analyses was within the CeA (Figure 5). In experiment 6 (anisomycin), the final numbers of rats in the shift-immediate, shift-delayed, consistent-immediate, and consistent-delayed conditions were 16, 16, 15, and 15, respectively. In experiment 7 (lidocaine), those sample sizes were 10, 8, 10, and 11, respectively. In experiment 8 (FCM), those sample sizes were 12, 12, 13, and 13, respectively.

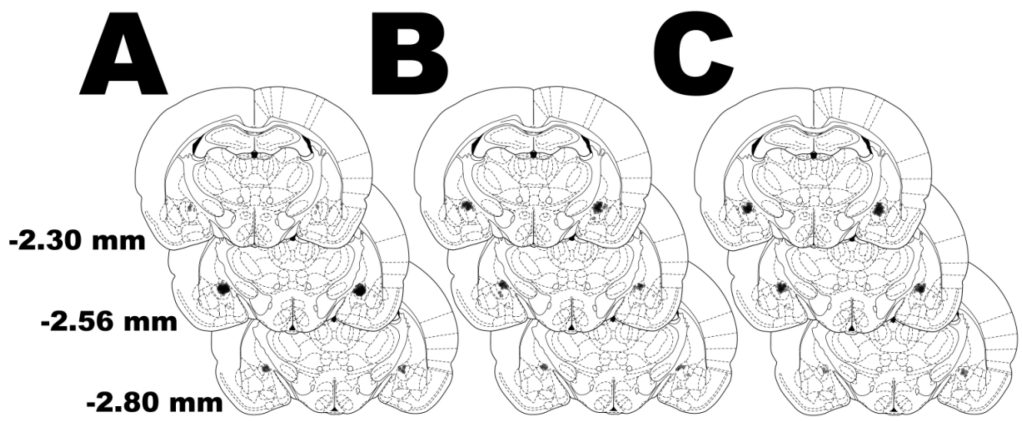


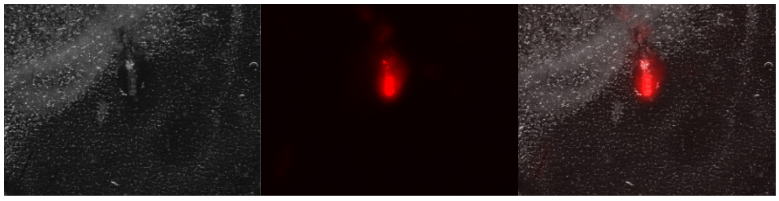
Figure 5. Schematic Representation of Injector Cannula Tip Placements for Rats Included in Experiment 6(A), Experiment 7(B), and Experiment 8(C).

The numbers on the right indicate distance (mm) from bregma along the rostrocaudal axis. For each placement, a single black dot of 50% opacity was drawn using Adobe Photoshop. Thus, darker areas indicate greater overlap.

Qualities of FCM spread. Injection sites in CeA varied across the mediolateral axis 2.2-2.6mm posterior to bregma, with minor dorsoventral variations. At the earliest timepoint, FCM above trace levels was detected only within the immediate proximity (~0.2 mm cylindrical radius) of the injector tract and tip (Figure 6). Generally, at 15 mins, the bulk of the FCM bolus extended radially ~0.5 mm from tips, but anisotropic diffusion was evident and the mediolateral position of the injection site primarily determined the ongoing course of dispersion. At subsequent time points, the concentrated mass of FCM tended to remain within that radius along the mediolateral and dorsoventral axes, but spread to variable extents along the rostrocaudal axis. Across 30 to 60 min time points, pools of FCM in CeA with similar intensity and expanse suggested sequestration occurred during that interval (c.f. Martin, 1991). FCM in CeA diminished by 90 mins, and was largely absent at 120 mins post-infusion.

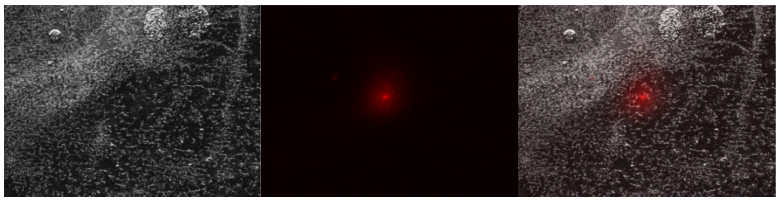
Much of the variability in the course of spread was attributable to the differential proximity of injection sites to the array of fiber bundles that surround and perforate CeA. These bundles, stria terminalis coursing through medial CeA, middle internal capsule/striatopallidal radiations spanning the dorsal border of CeA at a ventromedial-dorsolateral diagonal, and the intermediate capsule that partitions the lateral side of CeA from BLA, expedited FCM spread since diffusion along fibers is less tortuous than that which occurs through the neuropil (see Sykova & Nicholson, 2008 for review of diffusion factors in interstitial fluid). At the earliest timepoint, trace amounts of FCM could already be followed along various fiber tracts to distal locations, e.g. via stria terminalis to the bed nucleus. Trace amounts seemed to track numerous fiber bundles, including amygdalar pathways, but detection of trace amounts is not reliable, so I will not belabor. FCM injected into medial CeA more readily accessed stria terminalis, which accelerated diffusion to caudal CeA, and clearance, relative to lateral injections. The internal capsule focused spread, and as FCM hitched on stria, it diffused elliptically. By contrast, laterally injected FCM diffused spherically, and greater amounts of FCM appeared to sequester in CeA following lateral injections relative to medial injections. FCM was observed in intercalated cell masses, but there was scant evidence of diffusion into BLA. Instead, the intermediate capsule appeared to redirect FCM dorsally to ascend the external capsule. Injection sites in the center of the nucleus produced intermediate patterns of spread. NB: Although CeA architectonic subdivisions are not delineated by darkfield illumination, across the rostrocaudal range of injection sites, the medial subdivision (CeM) comprises the medial half of CeA, the capsular part (CeC) comprises the lateral portion abutting the intermediate capsule, and interposed between the two lies the lateral subdivision (CeL), which occupies the dorsocentral portion.

Time-point: 0 mins



Exposure: 500ms 1500ms

Time-point: 60 mins



Exposure: 500ms 1500ms

Figure 6. FCM Spread Examples

For each row, images depict darkfield (left), FCM (center), and an overlay of the two (right). The top row is a sample from time-point 0 mins, and the bottom row is from 60 mins (injection tip ~60µm caudal). Exposure times are identical and images were not altered. FCM infusions of 0.5µL (0.5 µg/ µL) were delivered over two minutes through 33GA (0.2mm O.D.; 0.1mm I.D) injector cannulae.

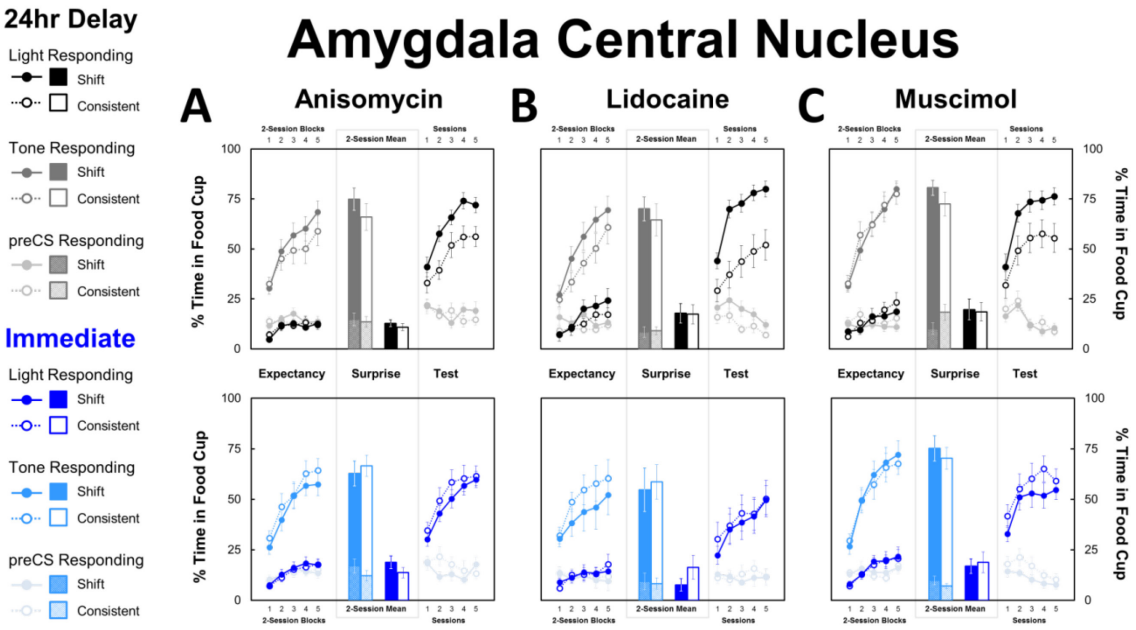


Figure 7. Conditioned Food Cup Responding for Experiments 6-8

Mean (± SEM) food-cup responding during pre-CS, light, and tone measurement epochs sequentially across all three phases (expectancy, surprise, and test) of experiment 6 (panel 7A) and experiment 7 (panel 7B), and experiment 8 (panel 7C). Analysis of expectancy and surprise phase data did not reveal major caveats: rats acquired and maintained comparably high levels of food-cup responding to the tone while exhibiting minimal conditioning to the light. The right side of each panel depicts the acquisition of food-cup responding over the course of the five test phase sessions. The heading of each panel identifies the drug (ANI, lidocaine, or FCM) that was infused into CeA (see text for details). Immediate (bottom; blue), but not delayed (top; grayscale), post-surprise session infusions of anisomycin in experiment 6 (Fig. 7A), lidocaine in experiment 7 (Fig. 7B), and FCM in experiment 8 (Fig. 7C) each eliminated the shift group advantage in learning about the light.

Behavioral results. Figure 7 depicts food-cup responding during pre-CS, light, and tone measurement epochs sequentially across all three phases (expectancy, surprise, and test) of experiment 6 (panel 7A), experiment 7 (panel 7B), and experiment 8 (panel 7C).

Expectancy phase. In each Fig. 7 panel, the leftmost portion shows that within each of the three experiments, all groups of rats acquired comparably high levels of food-cup

responding to the tone while exhibiting minimal conditioning to the light. For each experiment, behavioral condition (shift vs. consistent) x subsequent drug treatment (immediate vs. delayed: anisomycin in experiment 6, lidocaine in experiment 7, FCM in experiment 8) x two-session block (1-5) ANOVAs were performed on data from each measurement epoch (pre-CS, light, and tone). No significant effects or interactions (*P*s > 0.074) were observed for any variable in any of the three experiments aside from the effect of block on pre-CS responding in experiment 8 ($\varepsilon = 0.94$, $F_{4, 232} = 2.47$, $P = .049$) and the pervasive effects of block on responding during the light (*P*s < .001) and tone (*P*s < .001). Additional behavioral condition x subsequent drug treatment ANOVAs of performance over the final two sessions of the expectancy phase found that in experiment 8, the effect of drug treatment on responding to the light was significant ($F_{1, 58} = 4.70$, $p = 0.034$), but the slightly greater responding by immediate rats can be ignored. No other effects (*P*s > .099) or interactions were significant (*P*s > .183). Thus, within each experiment, rats in all groups entered the surprise phase with similar levels of responding.

Surprise phase. The bars in Fig. 7 depict food-cup response means collapsed across the two surprise phase sessions. For each experiment, data from each of the three measurement epochs were subjected to behavioral condition x drug treatment ANOVAs. In experiment 6, there were no significant effects of drug treatment on pre-CS responding ($F_{1, 58} = .029$, $P = .865$), responding during the light ($F_{1, 58} = 3.45$, $P = .068$), or responding during the tone ($F_{1, 58} = .933$, $P = .338$). There were no effects of behavioral condition (*P*s >.145), and the behavioral condition x drug treatment interaction was not significant for any measure (*P*s >.289). In experiment 7, there were no significant effects of drug treatment on pre-CS responding ($F_{1, 35} = .001$, $P = .990$), responding during the light ($F_{1, 35} = 1.24$, $P = .274$), or

responding during the tone ($F_{1, 35} = 1.64$, $P = .208$). There were no effects of behavioral condition (*P*s >.418), and the behavioral condition x drug treatment interaction was not significant for any measure (*P*s >.369). In experiment 8, no effects of drug treatment (*P*s >.497) or behavioral condition (*P*s >.240) were significant for responding during either cue, nor did those variables interact (*P*s >.753). Thus, within each experiment, rats in all groups began the test phase after showing similar levels of responding to both the light and tone during the surprise phase.

Test phase. The rightmost portion of each Fig. 7 panel shows the primary data of this study, the acquisition of food-cup responding to the light during the test phase. Mixed, repeated-measures ANOVAs on light and pre-CS responding consisted of the between-subjects variables of behavioral condition and drug treatment, and the within-subjects variable of test sessions (1–5) with Greenhouse–Geisser correction.

Immediate, but not delayed, post-surprise session infusions of anisomycin in experiment 6 (Fig. 7A), lidocaine in experiment 7 (Fig. 7B), and FCM in experiment 8 (Fig. 7C) each eliminated the shift condition advantage in learning about the light. The behavioral condition x drug treatment interaction was significant for experiment 6 ($F_{1, 58} = 5.35$, $P = .024$), experiment 7 ($F_{1, 35} = 5.07$, $P = .031$), and experiment 8 ($F_{1, 46} = 4.75$, $P = .035$). Furthermore, for all three experiments, delayed rats in the shift condition showed significantly greater responding than either delayed rats in the consistent condition (*Ps* < .040) or immediate rats in the shift condition (*Ps* < .031). No difference was supported between treatment groups in the consistent condition (*P*s < .418) or between behavioral groups that were infused immediately after surprise sessions with anisomycin ($P = .421$), lidocaine ($P = .735$), or FCM ($P = .339$).

Analyses of pre-CS responding in the test phase did not reveal any major caveats. In experiment 6, the significant effect of session ($\varepsilon = 0.83$, $F_{4, 232} = 3.35$, $P = .016$) interacted with behavioral condition ($\varepsilon = 0.83$, $F_{4, 232} = 3.09$, $P = .024$), but no other effects (Ps > .421) or interactions were significant (Ps > .107). In experiment 7, the behavioral condition x session interaction was significant ($\varepsilon = 0.868$, $F_{4, 140} = 2.72$, $P = .040$), but the effect of session was not reliable ($\varepsilon = 0.868$, $F_{4, 140} = 2.34$, $P = .068$) and no other effects (Ps > .135) or interactions were significant (Ps > .116). In experiment 8, the effect of session was significant ($\varepsilon = 0.749$, $F_{4, 184} = 14.39$, $P = .001$), but ANOVA did not find any other reliable effects (Ps > .158) or interactions (Ps > .339).

Discussion

The results of these studies demonstrate the importance of intact CeA function during the consolidation of α_{Light} memories. Infusions of anisomycin (experiment 6), lidocaine (experiment 7), or FCM (experiment 8) immediately, but not 24 hrs, after surprise phase sessions abolished the enhanced learning observed for shift group rats. Taken together, it appears evident that CeA post-session activity over some duration that spans less than 24hrs is critical for α_{Light} values that are increased during the surprise phase to be stored and used later in the test phase to facilitate light-food learning. We first describe a few mechanisms whereby the disruptions incurred in these studies would suffice to interfere with consolidation. Then, we discuss the implications of these results for brain systems that modulate α.

Mechanisms disrupting CeA-dependent consolidation

A simple interpretation of the results of Experiment 6, consistent with the logic of protein synthesis inhibition studies, is that surprise induces a cascade of events that normally culminates in structural change in CeA corresponding to an altered α_{Light} memory. However, prior observations of the limited necessity of CeA function in this task (Holland & Gallagher, 2006) and the results of Experiments 7 and 8 argue against this canonical interpretation.

As noted in chapter [1], if CeA (or any brain region) was a critical locus of altered α_{Light}, accelerated learning about the light would require access to that memory. The findings of Holland and Gallagher (2006) suggest that CeA is not a critical locus: NBQX infusions into CeA prior to surprise sessions prevented the shift group advantage, but the same manipulation prior to test phase sessions did not affect light-food learning. Thus, normal CeA function appears unnecessary for expression of α_{Light}. However, anisomycin is used in behavioral neuroscience to support arguments of memory substrates, so the retrieval of an essential α_{Light} memory stored in CeA may have been robust to the AMPA/kainite-receptor antagonism achieved in Holland & Gallagher (2006). Instead, the results of experiments 7 and 8 support an alternative explanation of experiment 6.

Anisomycin and other nonspecific protein-synthesis inhibitors interfere with consolidation through translational inhibition (Davis & Squire, 1984; Kandel, 2001; Dudai, 2004; Sutton & Schuman, 2006; Costa-Mattioli et al., 2009), but they also cause extensive proteomic alterations that confound most *in vivo* studies (Routtenberg & Rekart, 2005; Gold 2006; 2008; Rudy, 2008; c.f. Alberini, 2008; Hernandez & Abel, 2008). For example, anisomycin is capable of rapidly eliciting persistent neurophysiological dysfunction as a

potent agonist of p38, ERK, and JNK mitogen-activated protein kinase (MAPK) cascades (Radulovic & Tronson, 2008). These MAPK cascades exert bidirectional control over neuronal excitability (e.g. Costello & Herron, 2004; Poolos et al., 2006; Schrader et al., 2006; Wu et al., 2011) via fast cytoplasmic protein/protein interactions and slower transnuclear mechanisms. Stimulation of MAPK cascades by anisomycin *in vitro* occurs prior to and perhaps independently of translational inhibition (Mahadevan & Edwards, 1991; Edwards & Mahadevan, 1992; Shifrin & Anderson, 1999; Torocsik & Szeberenyi, 2000).

Potent cascade activation by anisomycin is problematic for interpretation of the results of experiment 6, as CeA may not contribute to the consolidation of α_{Light} memories, but essential processes elsewhere may be sensitive to profoundly abnormal CeA activity (see Canal et al., 2007; Gold, 2008; Rudy, 2008). That is, the mechanism of disruption in experiment 6 may simply reduce to the introduction of excessive noise. In support of that view, in an unrelated conditioning preparation, intra-amygdalar pretreatment with the anesthetic lidocaine attenuated anisomycin-induced amnesia, without affecting consolidation when delivered alone (Sadowski et al., 2011). Parsimony suggested that anisomycin produced amnesia primarily through stimulation of irregular or hyper neuronal activity, which lidocaine allayed.

We first sought to address that confound in Experiment 7 by infusing lidocaine into CeA after surprise sessions, which was expected to reduce post-session CeA neural activity without interfering with translational activity induced by cascades initiated during the surprise sessions themselves. A null effect of these infusions would have set the stage for a subsequent examination of the effects of lidocaine pretreatment on the effects of anisomycin infusions. However, in Experiment 7, intra-amygdalar infusions of lidocaine alone after

surprise sessions prevented surprise-induced enhancements in cue associability, thereby implicating post-session CeA neuronal activity as critical to consolidation of alpha memories. We confirmed and extended that implication in experiment 8 by demonstrating comparable effects of post-surprise inactivation of CeA with fluorescent muscimol, a $GABA_A$ agonist, which spares conductance along fibers of passage. Time-coursed assessment of FCM spread following CeA infusion suggested that the principal site of drug action was largely constrained to the nucleus.

Implications for α modulation brain systems

The results reported here demonstrate that post-surprise session CeA activity is necessary for the consolidation of α_{Light} memories, but, as noted in the previous section, CeA ostensibly mediates this consolidation without contributing a locus for storage. We therefore assume that α_{Light} memories are stored elsewhere, most plausibly in frontoparietal associated attention networks. However, CeA projection targets are strictly subcortical (Pitkanen, 2000), so access to frontoparietal cortical systems must be indirect. In what follows, we relate CeA activity to those candidate loci through direct paracrine and neurocrine signaling interactions of this nucleus with intermediary regions.

Role for amygdalar protein translation processes

Disruptive effects of anisomycin infusions does not demand involvement of amygdalar translational processes in the storage of α_{Light} memories, but we do not deny a potential role for such processes in mediating consolidation elsewhere. Notably, considerable numbers of CeA perikarya display immunoreactivities for notable signal peptides that include neurotensin (NT), corticotropin-releasing factor (CRF), somatostatin (SOM), substance P (SP), dynorphins (DYN), leu and met-enkephalin (ENK), and galanin (GAL)

(Ljungdahl et al., 1978; Roberts et al., 1982; Wray & Hoffman, 1983; Fallon & Leslie, 1986; Cassell & Gray, 1989a; reviewed in Gray, 1988). Nonspecific translational inhibition by ribosomal binding of anisomycin affects *de novo* synthesis of precursors for these signal peptides in addition to proteins that underlie persistent plasticity. Exocytosis of those peptides packaged in dense core vesicles (e.g. Treweek et al., 2009) requires sustained burst firing, which should be sensitive to the pharmacological manipulations used in this study. Thus, the mechanism underlying consolidation of α_{Light} memories might depend upon the release of signal peptides by CeA neurons, and replenishing those resources may be necessary for subsequent iterations ("consolidation waves") that occur within 24 hours (e.g. Sara, 2010). The molecular constituents of CeA output during consolidation are likely diverse since many CeA neurons express multiple signal peptide families (Shimada et al., 1989; Gray & Magnuson, 1992; Marchant et al., 2007; Poulin et al., 2008; Reyes et al., 2008; Olucha-Bordonau et al., 2015), and several emit amygdalofugal efferents (Uhl et al., 1978; Uhl & Snyder, 1979; Palkovits et al., 1981; Higgins & Schwaber, 1983; Veening et al., 1984; Moga & Gray, 1985; Cassell et al., 1986; Sakanaka et al., 1986; Gray & Magnuson, 1987a; 1987b; Rao et al., 1987; Gray & Magnuson, 1992; Vankova et al., 1992; Fendt et al., 1997; Saha et al., 2002; Tjoumakaris et al., 2003; Reyes et al., 2008; 2011).

CeA projection systems and α memory consolidation

In this section we first detail the projection profile of CeA and then offer a set of consolidation mechanisms that include specific peptidergic actions of CeA. The set emphasizes separable interactions that may be valid components of an integrated process of α memory change, aspects of which may extend to the consolidation of other types of memories.

CeA gains indirect access to the entire cortical mantle through its subcortical efferents. Dense limbic forebrain projections from CeA innervate nearby sublenticular cholinergic SI/nBm, interstitial nucleus of the posterior limb of the anterior commissure (IPAC; overlaps with fundus striatum), and bed nucleus of the stria terminalis (Petrovich & Swanson, 1997; Dong et al., 2001; Gastard et al., 2002; Jolkkonen et al., 2002). These regions unite with CeA to comprise a mesocircuit termed the *central extended amygdala* (Alheid et al., 1995; DeOlmos & Heimer, 1999; Alheid, 2003). This mesocircuit contains the densest concentration of neuropeptidergic cells outside of the hypothalamus (Gray, 1988; Olucha-Bordonau et al., 2015). Moreover, members of the system are the only known extrinsic target of CeA fibers that contain ENK (Uhl et al., 1978; Palkovits et al., 1981; Moga & Gray, 1985; Gray & Magnuson, 1987a; Rao et al., 1987; Gray & Magnuson, 1992; Tjoumakaris et al., 2003), and evidence suggests that CeA may also release NT, CRF, and SP onto those regions (Uhl & Snyder, 1979; Sakanaka et al., 1981; Sakanaka et al., 1986).

Additionally, CeA emits substantial descending projections that traverse lateral hypothalamus (LH) to innervate a variety of noteworthy areas in the midbrain, pons, and medulla (Price, 2003). Figure 8 below depicts this pathway. Except for ENK, all of the aforementioned CeA signal peptides (NT, CRF, SOM, SP, DYN, and GAL) have been observed to varying extents in specific amygdalofugal brainstem terminals. Upon entering tuberal hypothalamus, some varicose fibers of this descending pathway diverge medially to innervate dorsal hypothalamic area, dorsomedial hypothalamic nuclei and paraventricular hypothalamic nuclei (Gray et al., 1989; Rosen et al., 1991; Marcilhac & Siaud, 1997; Myers et al., 2014). Many efferents enmesh densely orexigenic hypothalamic districts, including perifornical area to appose orexin neurons (Yoshida et al., 2006), and some form a plexus at

parasubthalamic nucleus (Petrovich et al., 2001), but the majority of fibers concentrate before perforating ventral tegmental area (VTA) via the ventrolateral aspect of the medial forebrain bundle (Rosen et al., 1991; Wallace et al., 1992).

As this descending pathway negotiates the midbrain, fibers splay dorsolaterally to provide *en passant* and punctate input to dopaminergic SNcl (A9) and rostral VTA (non-midline portions of A10) (Gonzales & Chesslet, 1990; Wallace et al., 1992; Geisler & Zahm, 2005; Kaufling et al., 2009; Jhou et al., 2009; Zahm et al., 2011). Through the release of NT, CeA may increase the excitability of dopaminergic neurons in SNcl (Vankova et al., 1992; Binder et al., 2001), but probably not those in VTA (Zahm et al., 2001). Most fibers of the pathway continue by cornering the lateral edge of medial lemniscus to enter central tegmental field (CTF) bearing dorsomedially towards periaqueductal gray (PAG) (Krettek & Price, 1978; Rosen et al., 1991). Projections descend through pons along a ventrolateral to mediodorsal orientation with many fibers terminating in retrorubral field (A8), pontine reticular formation, ventrolateral PAG, and dorsal raphe (A10dc) (Rosen et al., 1991; Wallace et al., 1992; Fendt et al., 1997; Peyron et al., 1998; Zahm et al., 2011). In more caudal hindbrain, CeA terminal fields ramify extensively upon parabrachial nuclei, mesencephalic nucleus of the trigeminal nerve, rostral locus coeruleus (LC; A6) and peri-LC areas rich in neuropeptide-S (NPS) expressing cell bodies, dorsal vagal complex (DVC; A2/C2), and rostral ventrolateral medulla (A1/C1) (Veening et al., 1984; Moga & Gray, 1985; Gray & Magnuson, 1987b; Cassell & Gray, 1989b; Danielsen et al., 1989; Thompson & Cassell, 1989; Wallace et al., 1992; Pickel et al., 1995; 1996; Petrovich & Swanson, 1997; Van Bockstaele et al., 2001; Saha et al., 2005; Xu et al., 2007; Kang & Lundy, 2009; Reyes et al., 2011; Schwarz et al., 2015). Considering functions of these efferent regions, it is unlikely that CeA input to

each of them is necessary for the consolidation of α_{Light} memories, but we surmise plausible interactions with many (SI/nBm, orexigenic LH, SNcl, LC, NPS). For example, CeA efferents carrying CRF to peri-LC (Van Bockstaele et al., 2001; Reyes et al., 2011; McCall et al., 2015) may modulate activity of noradrenergic LC and NPS-expressing neurons during consolidation (c.f. Xu et al., 2004; Okamura et al., 2011; Jungling et al 2012).

Surprise is a multifarious construct, and delineating its sequellae facilitates analogies with more general descriptions of CeA function (e.g. LeDoux, 2012). Indeed, aspects of surprise may be considered motivational events. For example, it operates as a psychological stressor if it challenges or invalidates components of a world model that an animal relies heavily upon for survival (c.f. Valentino & Van Bockstaele, 2008; Arnsten, 2009). In less dire situations, surprise may simply invigorate an animal by signifying an opportunity to procure novel information and therefore encourage exploration of the environment (Sokolov, 1963). Regardless of the affective valence, registering surprise will likely increase arousal, which in turn partly determines the efficacy of consolidation. Perhaps CeA responds to surprise through its widespread access to vigilance centers (Gallagher & Holland, 1994), e.g. cholinergic (Dringenberg and Vanderwolf, 1997; Jones, 2008; Gozzi et al., 2010), orexigenic (Wheeler et al., 2014; Sakurai, 2014), and noradrenergic systems (Aston-Jones & Cohen, 2005; Sara, 2009; Carter et al., 2010; Sara & Bouret, 2012; McCall et al., 2015), to induce a state of generalized arousal (c.f. Moruzzi & Magoun, 1949; Kapp et al.,1992; Phelps & LeDoux, 2005). If so, CeA activity might continue to influence consolidation post-session by maintaining or reiterating components of such a global organismic state.

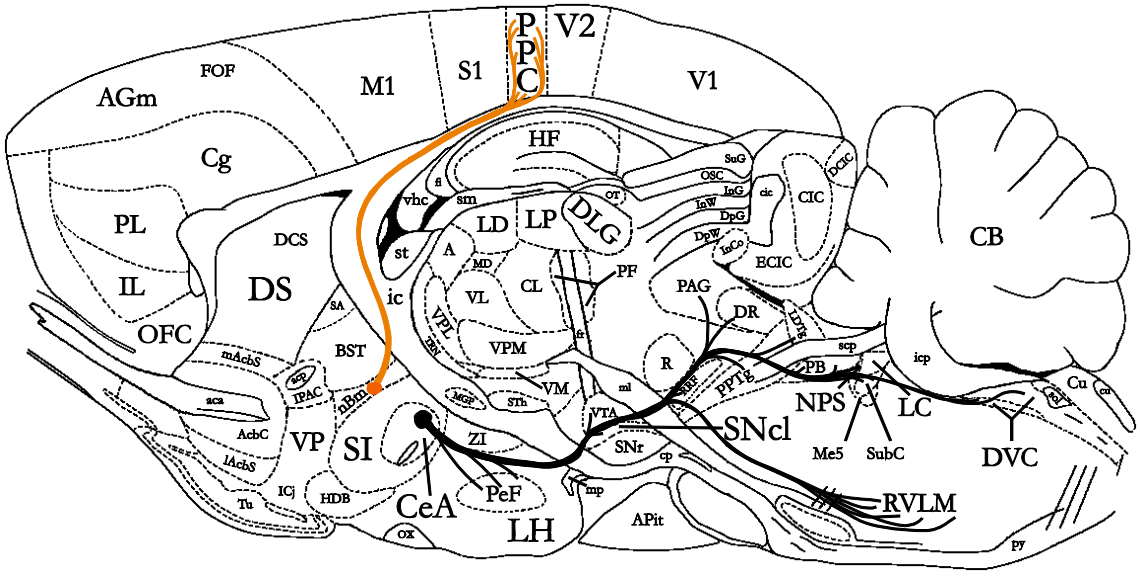


Figure 8. Schematic Depiction of CeA Descending Efferent Pathway

CeA brainstem projections (black), cholinergic innervation of PPC (orange). To depict regions of interest, this figure was adapted from an amalgam of Paxinos & Watson (1998) sagittal slices. It is not to scale, but I attempted to approximate axial relations.

Chapter 5:

Summary

This thesis expands our characterization of brain circuitry that implement attention to facilitate learning according to Pearce & Hall (1980) rules. Chapter 2 establishes PPC as a candidate locus for α_{Light} memory storage by demonstrating its importance during encoding, consolidation, and expression, Chapter 3 reports that V2 activity was important for expression, but not encoding, and Chapter 4 suggests that post-session functions of CeA are required for the consolidation of surprise increased α. As reviewed earlier, our working PH circuit model separated the subsystem responsible for α increments into encoding and expression modules, and was agnostic about storage. In the model, prediction error computations that support α updating rely upon cooperation of CeA and SNcl, and innervation of PPC by cholinergic SI/nBm is required for updated α to enhance new learning. The results of this thesis inform considerations of potential α memory storage sites, contribute a novel component to the expression module, and extend the role of CeA into domains of consolidation.

A range of neuropsychological functions have been ascribed to primate PPC, including operations involved in economic and perceptual decision-making (Platt & Glimcher, 1999; Glimcher, 2003; Gold & Schadlen, 2007; Kable & Glimcher, 2009), abstract categorization (Freedman & Assad, 2011), numerousity judgments (Dehaene et al., 2003; Hubbard et al., 2005; Nieder & Dehaene, 2009; Roitman et al., 2012; Harvey et al., 2013), planning and selection of actions (Mountcastle et al., 1975; Andersen & Bueno, 2002; Culham & Valyear, 2006; Andersen & Cui, 2009), episodic and working memory (Wagner et

al., 2005; Cabeza et al., 2008; Hutchinson et al., 2009; Rawley & Constantinidis, 2009; Berryhill, 2012), and the control of visuospatial attention (Colby & Goldberg, 1999; Corbetta & Shulman, 2002; Assad, 2003; Yantis & Serences, 2003; Behrmann et al., 2004; Chambers & Mattingley, 2005; Gottlieb, 2007; Bisley & Goldberg, 2010; Pessoa et al., 2010; Petersen & Posner, 2012). Much of that diversity is attributable to the fact that PPC is an axial description of a large swath of primate cortex, and the region has been parceled for both macaque (Colby et al., 1988; Cavada & Goldman-Rakic, 1989a; 1989b; Andersen et al. 1990, Lewis & Van Essen, 2000a; 2000b) and human (Zilles & Palomero-Gallagher, 2001; Rushworth et al., 2006; Scheperjans et al., 2008a; 2008b; Silver & Kastner, 2009). Some of the more specialized subregions appear to support homologous functions across primates (Wise et al., 1997; Rizzolatti et al., 1998; Rizzolatti & Luppino, 2001; Culham & Kanwisher, 2001; Van Essen, 2004; Grefkes & Fink; 2005).

By contrast, rat PPC is a sliver of cortex, separable anatomically into medial and lateral PPC (Reep & Corwin, 2009; Wilber et al., 2014a). Even so, functions in allocentric spatial navigation (Nitz, 2009; 2012; Whitlock et al., 2008; 2012; Whitlock, 2014, Wilber et al., 2014b), decision-making (Raposo et al., 2014; Hanks et al., 2015), working memory (Myskiw & Izquierdo; 2012), overt orienting (Reep & Corwin, 2009), and attention for learning (Bucci, 2009) have been described. Our demonstration that rat PPC may store a memory parameter for the control of attention provides an additional data point for arguments of broadly analogous functions across species. It would be of interest to search for correlates of a rat version of attentional priority maps to strengthen that assertion.

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University of Delaware, Newark, DE	B.A.	2009	Behavioral Neuroscience
Johns Hopkins University, Baltimore, MD	M.A.	2012	Behavioral Neuroscience
Johns Hopkins University, Baltimore, MD	Ph.D	2012-pres.	Behavioral Neuroscience

Positions

Occupation	Start (mm/yy)	End (mm/yy)	Field of Study	Institution	Supervisor
Research Assistant	03/06	06/06	Emotion Psych.	University of Delaware	Dr. Cal Izard
Science and Eng. Scholar	06/07	08/07	Behav. Neuro.	University of Delaware	Dr. Mark Stanton
Research Assistant	08/07	05/09	Behav. Neuro.	University of Delaware	Dr. Mark Stanton
Amgen Scholar	06/09	08/09	Mol. Biology	U of California at SF	Dr. Ying-Hui Fu & Dr. Louis Ptacek
Lab Manager/ Research Associate	08/09	08/10	Behav. Neuro.	University of Delaware	Dr. Mark Stanton
Predoctoral Student	08/10	Present	Behav. Neuro.	Johns Hopkins University	Dr. Peter Holland
Research Volunteer	06/14	Present	Behav. Neuro.	National Institute on Drug Abuse	Dr. Geoff Schoenbaum Dr. Yeka Aponte

Research Papers

Schiffino, F. L., & Holland, P. C. *submitted to Neurobiology of Learning and Memory*. Consolidation of a memory that guides attention for learning depends upon amygdala central nucleus activity.

Schiffino, F. L., & Holland, P. C. *submitted to European Journal of Neuroscience*. Perturbed activity of rat extrastriate cortex disrupts the expression, but not encoding, of a memory that guides attention for learning.

Asem*, J. S. A., **Schiffino*, F. L.**, & Holland, P. C. (2015). Dorsolateral striatum is critical for the expression of surprise-induced enhancements in cue associability. European Journal of Neuroscience, 42, 2203–2213.

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