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Contribution of the dorsolateral prefrontal cortex to attentional and mnemonic processes in visual search

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

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CONTRIBUTION OF THE DORSOLATERAL PREFRONTAL CORTEX TO ATTENTIONAL AND MNEMONIC PROCESSES IN VISUAL SEARCH

(Thesis Format: Monograph)

by

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Graduate Program in Neuroscience

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Neuroscience

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Abstract

A key characteristic of selective visual attention is that it may be deployed on the basis of our knowledge or goals of the task at hand. Here, we used cryogenic deactivation to investigate the contribution of the dorsolateral PFC to cognitive flexibility and working memory, as well as their relation to the deployment of attention. Macaque monkeys performed visual search tasks requiring them to foveate a target in an array of stimuli. These included a feature search, a constant-target conjunction search, a variable-target search and variable-target with delay search task, with each being more cognitively demanding than the last. Bilateral deactivation of the DLPFC during more demanding tasks resulted in increased reaction time and decreased accuracy. These effects on visual search performance suggest that the DLPFC is involved in the deployment of attention to a target, and also contributes to the flexible and mnemonic processes needed when task demands increase.

Keywords

DLPFC, visual search, working memory, task-set reconfiguration, behavioural flexibility, cortical cooling

Co-Authorship Statement

Dr. Kevin Johnston was the principal investigator and supervisor for the study described in this thesis. Dr. Johnston conceived and designed the visual search paradigms used in this thesis. Dr. Johnston wrote the code for the behavioural data analysis, though I was responsible for all data collection and analysis thereafter.

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Introduction

Imagine you are looking at playing cards spread face up on a table, and your goal is to find the Queen of Spades. Although all of the cards are in plain view, searching from one card to the next is necessary to locate the correct one. Looking for this card is an example of a conjunction search in which two features define the target, in this case the value of the card and the suit. To narrow our search we can direct our attention to relevant target features, such as to all cards that are Queens or all cards that are Spades. We can end our search and identify the target card when what we are looking at is a Spade and also a Queen, thus matching the features we were searching for, and correctly identifying the Queen of Spades. This is the process of selective visual attention.

A prerequisite for successful visual behaviour is the ability to selectively attend to relevant stimuli, while ignoring irrelevant ones. Attention is the process of filtering irrelevant information to focus on more behaviourally relevant information. Given the inherent demand for processing resources, the visual system cannot fully process the entirety of the visual field (Tsotsos 1990). As a result of this demand, only a small area of the visual field can be processed to higher order brain areas (Wolfe 1994). This area of the visual field from which information is further processed comes from the high-resolution area of the retina, the fovea. Foveal vision occupies only about 1% of our visual field but already a much larger amount (up to 50%) in our primary visual cortex (Horton and Hoyt 1991). Since the majority of our visual information comes from foveal input, relocating the fovea to relevant stimulus locations is essential, and thus movements of the eyes direct the fovea toward objects of interest to facilitate detailed visual processing (Findlay 2009). The most common type of eye movement is called a saccade, which is a fast ballistic movement of the eye to redirect the fovea to a new location (Gilchrist 2011). When scanning a visual scene, saccades (interrupted by fixations) redirect our gaze up to several times a second and are crucial to gather more information from the visual environment. Though this is typically how visual information is gathered, attention can also be directed without movements of the eyes (covert attention; Posner 1980). Fixation on an object allows the image of that object to fall on the fovea for visual information to be processed, while saccades continue to relocate our fovea to different aspects of the scene.

Visual attention is understood to be deployed on the basis of both bottom-up and top-down processes. Bottom-up processes consist of the distinctiveness of particular stimuli in the environment, while top-down processes comprise the knowledge and goals of the observer (Wolfe 1994, Miller and Cohen 2001, Bundesen *et al.* 2005, Hamker 2006, Wolfe 2010). Stimuli that are salient or perceptually different compared to neighbouring stimuli, seem to automatically draw our attention (Wolfe 1994). An item containing a unique feature, such as colour, shape or a particular orientation, increasingly draws our attention the greater the difference between it and objects around it. The role of bottom-up attention can be demonstrated in searching for a target defined by a single feature, known as a feature search. An example of this would be looking for a red stimulus on a screen full of green stimuli. The oddball red stimulus is distinctive on the screen, and the target can be located without prior knowledge of its features. Top-down attention on the other hand involves directing attention towards objects of interest, and can help locate targets that may not be visually distinctive from the distractors. Although locating a red stimulus among green ones can be driven by bottom-up attention, searching for a target defined by multiple features requires prior knowledge. Searching for a target defined by two features (such as colour and shape) is known a conjunction search, such as a red square among red and green squares and circles. The target now shares features with the distractors, as a red square would be the same colour as a red circle distractor, and the same shape as a green square distractor. Since all stimuli in a conjunction search are perceptually similar, one must know what the target is in order to find it, which is similar to locating the Queen of Spades in a pile of cards. This prior knowledge can be in the form of a memory representation of the target following instruction (Bichot and Schall 1999b), or can be drawn upon given verbal direction (Yarbus 1967). Prior knowledge can also be used to override bottom-up attentional processes during search for a single unique stimulus (Bichot *et al.* 1996). This demonstrates that in addition to being driven by bottom-up processes, attention can also be allocated using top-down control.

Eye movements facilitate more detailed visual processing and may thus be considered an overt form of selective visual attention (Findlay & Gilchrist 2003, Findlay 2009). While covert attention can direct attention without deploying an eye movement, an eye movement cannot be directed to one location while attention is directed to another (Deubel and Schneider 1996, Hoffman and Subramaniam 1995, Findlay & Gilchrist 2003). The fundamentals of this obligatory relationship between eye movements and attention, however, are somewhat debatable (see review, Smith and Schenk 2012). The premotor theory of attention proposes that attention is actually a consequence of the motor preparation for an eye movement (Rizzolatti *et al.* 1987), which can result in attention preceding to the target location ahead of the fovea (Hoffman and Subramaniam

1995). As demonstrated earlier, eye movements are crucial to gathering more information about the visual environment. Saccades help direct attention to different aspects of a visual scene, while something that draws our attention in the visual field results in an orienting saccade to place the fovea on it and examine this stimulus further. Enhanced perceptual discrimination at the target location of the upcoming saccade demonstrates the influence of eye movements on attention (Deubel and Schneider 1996); while attention can also influence saccades, such as distracting stimuli affecting saccade latency (Walker *et al.* 1997). The fact that eye movements and attention are so intertwined and attention is potentially even a consequence of oculomotor system activation suggests the use of similar neural substrates or mechanisms.

Visual search tasks have been used extensively to investigate the neural basis of attention and cognitive processes related to the deployment of attention. In visual search tasks, the object is to locate a target from among non-target distractors (for review, see Wolfe 1998). Visual search paradigms can also be modified to investigate different cognitive functions. For example, the identity of the target and distractors can be altered to increase attentional demand. An example of a low-demand paradigm is a simple feature search where the target is defined by a unique feature (e.g. colour), and where attention can be guided to by way of bottom-up processes. In contrast, a conjunction search is an example of a more demanding task. This is demonstrated when a target is defined by a conjunction of features (e.g. colour and shape), in that the target not only shares some of the features with the distractors, but is also perceptually similar as well. As a result, top-down control using prior knowledge would now be needed to direct attention to the conjunction target. Prior knowledge can be a representation of the target (either defined by its features, or a picture-like representation) held as a target template to assist with top-down attention. Another cognitive process that can be tested in visual search is working memory. Working memory is the temporary retention of information to guide future behaviour (Baddeley 1992). At the beginning of a visual search task, target information (e.g. location, colour) can be briefly presented and subsequently followed by a blank-screen delay in which the subject must hold this target information in working memory. This information can then be used to guide attention to the target when the array is presented (Chelazzi *et al.* 1998, Woodman *et al.* 2007). Working memory of target location can also be tested by incorporating a delay after array presentation (Hasegawa *et al.* 2000, Iba and Sawaguchi 2002). Lastly, changing the search target or having multiple search targets in a visual search task can test cognitive or behavioural flexibility (Horowitz and Wolfe 2001, Bichot and Schall 2002, Rossi *et al.* 2007, Woodman *et al.* 2007). Altering the search target on a trial-by-trial basis requires subjects to now direct attention to the behavioural relevant stimulus using top-down control (Rossi *et al.* 2009). This includes updating the target template to the current search target on each trial. The target also may have been a distractor on the previous trial, making the task even more demanding as erroneous saccades are made to distractors that were targets on the previous day (Bichot and Schall 1999a).

Performance in visual search tasks is quantified by taking simple measurements, most commonly reaction time and accuracy (Wolfe 1998). Reaction time—the time between when the array is presented to the start of the saccade—is useful for determining the processing time of target selection. Two of these processes include discrimination of the target from distractors, and saccade programming to the target. A target more similar to distractors would take longer to identify, delaying this process and untimely delaying the reaction time. The percentage of trials in which the fovea lands at the target location, or the percentage of trials that a subject correctly identifies a search target as present in an array, is known as accuracy. By assessing reaction time and accuracy on different search paradigms, it can be determined how much the target stands out from distractors and insight can be gathered as to whether bottom-up attention guides the fovea to the target, or if it involves the direction of top-down attention. By making modifications to a visual search paradigm, it is useful to test processes besides visual attention, including working memory and cognitive flexibility (Wolfe 1994, Bundesen *et al.* 2005).

Though theories and models of attention are useful starting points, physiological data is needed to constrain them. It is beneficial that human studies can uncover functional areas underlying neural networks involved with attention and eye movements (Corbetta *et al.* 1998), but more invasive studies are needed to determine the neural mechanism of attention. This requires an appropriate animal model, the macaque monkey (*Macaca*). One of the highlighting factors that make these animals such useful models is that their brains are highly homologous to humans. This means that both macaque and human brains have many shared, derived characteristics from a common ancestor. This has been determined through cytoarchitecture studies examining cellular and brain layer composition and connectivity studies showing the similarity of brain connections to humans, in everywhere from the primary visual system to the prefrontal cortex (Kritzer and Goldman-Rakic 1995, Preuss 2007, Wise 2008, Passingham 2009). Their well-developed homologous visual system (Hubel and Wiesel 1977) and retinal similarity means they must also direct their fovea to objects of interest to facilitate visual processing. As rhesus macaques must orient their fovea in a similar manner to humans, including a large oculomotor range and saccade amplitude, they have a well-developed and well-studied oculomotor network. This network includes a number of interconnected cortical and subcortical brain areas, including the frontal eye field (FEF), supplementary eye field (SEF) and the lateral intraparietal area (LIP), all of which send projections to the common output target superior colliculus (SC), a midbrain structure connected to saccade motor generators (Selemon and Goldman-Rakic 1988, Johnston and Everling 2008, Johnston and Everling 2011, Curtis 2011). Again, comparative cytoarchitecture and functional MRI (fMRI) studies have determined homologues of these areas in the human brain (Petrides and Pandya 1999, Koyama *et al.* 2004, Baker *et al.* 2006). In addition, macaques' eye-movement repertoire is also very similar to humans, with only slight differences (Johnston & Everling 2008). As well, due to the oculomotor and saccade similarity with humans, macaques can be trained to perform many of the same eye movement tasks as humans. Single neuron recording in the awake macaque during eye movement tasks has allowed the correlation of neural activity with behaviour to better understand the neural basis of attention (e.g. Bisley and Goldberg 2003). By using the rhesus macaque as a model, researchers can manipulate eye movement tasks to examine many cognitive processes.

From comparative anatomical and neurophysiological studies of macaques performing visual search tasks, a network of cortical and subcortical areas has been shown to overlap with the oculomotor network, areas responsible for eye movements and voluntary shifts in attention towards objects of interest. This network consists of several inter-connected areas, including the FEF (Bichot and Schall 1999a, Schall 2002), area

LIP (Ipata *et al.* 2006, Thomas and Pare 2007) and the SC (Shen *et al.* 2011). Neuroimaging studies have identified similar brain regions and corresponding areas of activation in human participants, known as the dorsal frontoparietal attention network (Corbetta *et al.* 1998, Corbetta & Shulman 2011). Single-unit neuronal recordings have found neurons in these areas that exhibit activity consistent with the correct selection of a target in visual search. Their activity profile is as follows: immediately following presentation of the stimulus array, neurons that have a stimulus in their response field (the location in the visual field that they represent) have an initial, indiscriminate increase in activity (see Figure 1). Depending on whether this stimulus is a target or a distractor, the neuron's activity will subsequently be enhanced or attenuated, respectively (e.g. Schall 2002). Similar activity is seen throughout this network; the FEF, SC and area LIP (Schall 2002, Thomas and Pare 2007, Shen *et al.* 2011). The common idea is that all stimuli in the visual environment compete for our attention, while only those neuron's activity representing stimuli that are behaviourally relevant are enhanced, and all others are filtered out. Current theories of visual attention also propose the existence of a visual priority map that represents all stimuli in our visual field (also referred to as a salience map, see Figure 2; Olshausen *et al.* 1993, Wolfe 1994, Itti and Koch 2001, Bundesen *et al.* 2005, Thompson and Bichot 2005, Fecteau and Munoz 2006, Hamker 2006, Bisley and Goldberg 2010, Jerde and Curtis 2013). Each stimulus in this priority map is thought to have an attentional weight assigned to it based on bottom-up factors (how unique it is) and top-down factors (how behaviourally relevant it is). After each stimulus has been assigned its attentional weight, the stimulus with the highest activation on the map is chosen as the next target of selection in a winner-take-all approach. This map is thought not to exist at only a single location, but is in fact instantiated in each of the areas of the oculomotor network (Kusunoki *et al*. 2000, Schall 2002, Thompson and Bichot 2005, Fecteau and Munoz 2006, Thomas and Pare 2007, Shen *et al.* 2011), and possibly the pulvinar nucleus of the thalamus (Robinson and Petersen 1992, Bundesen *et al.* 2005). Since there appears to be top-down neural modulation (enhancement and attenuation of neural activity) based upon which stimuli are relevant, it is proposed that this represents top-down control from a higher-order area requiring knowledge of the target and task goals (Wolfe 1994, Miller & Cohen 2001, Bundesen *et al.* 2005, Hamker 2006). This area is the prefrontal cortex (PFC), which is the region thought to be one of the main control centers of the brain. To support this, human neuroimaging data also identified a frontal region involved in attention besides the above noted oculomotor network, which is the dorsolateral PFC (DLPFC; Corbetta *et al.* 1998).

The DLPFC is thought to have influence over much of the brain due to its unique position and connections with important brain areas, and is thought to have involvement with many cognitive processes related to attention. These include functions such as attention, target selection, response suppression, decision making, task flexibility, and working memory. Attention—specifically visual attention—is thought to be controlled by the PFC (e.g. Hamker 2006). Cells in this area show filtering to spatially unattended targets, and even neuronal enhancement to attended stimuli (Everling *et al.* 2002). Lesions in macaques and human fMRI findings pinpointed the DLPFC as necessary on visual tasks that required top-down attentional control (Rossi *et al.* 2009). Working memory is a process that has been hallmarked by neural activity during a delay interval in a delayed response task, with this area possibly retaining or holding information during a

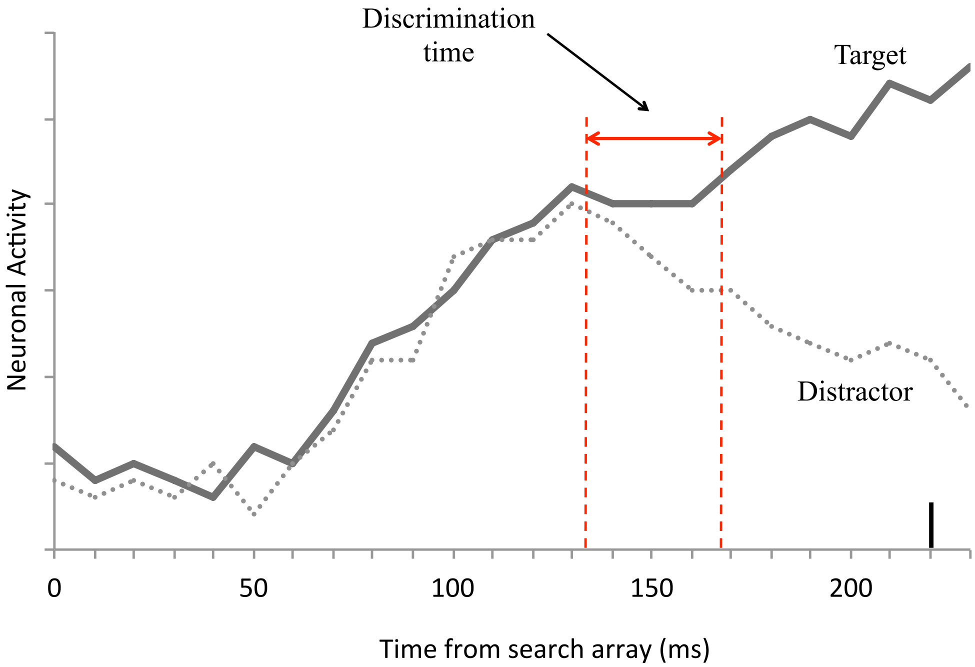

Figure 1. Neuronal activity during target selection. Illustration of neuronal activity in the oculomotor network when a target stimulus (solid line) or a distractor stimulus (dotted line) appears in the response field of a neuron. Initial increase in activity does not discriminate the target from a distractor. However, the target begins to be identified at the leftward red line, and target activity compared to distractor activity is statistically different by the rightward red line (discrimination time), signifying that the target is discriminated from the distractor. Once a certain saccade initiation threshold is reached, a saccade is executed (black vertical line).

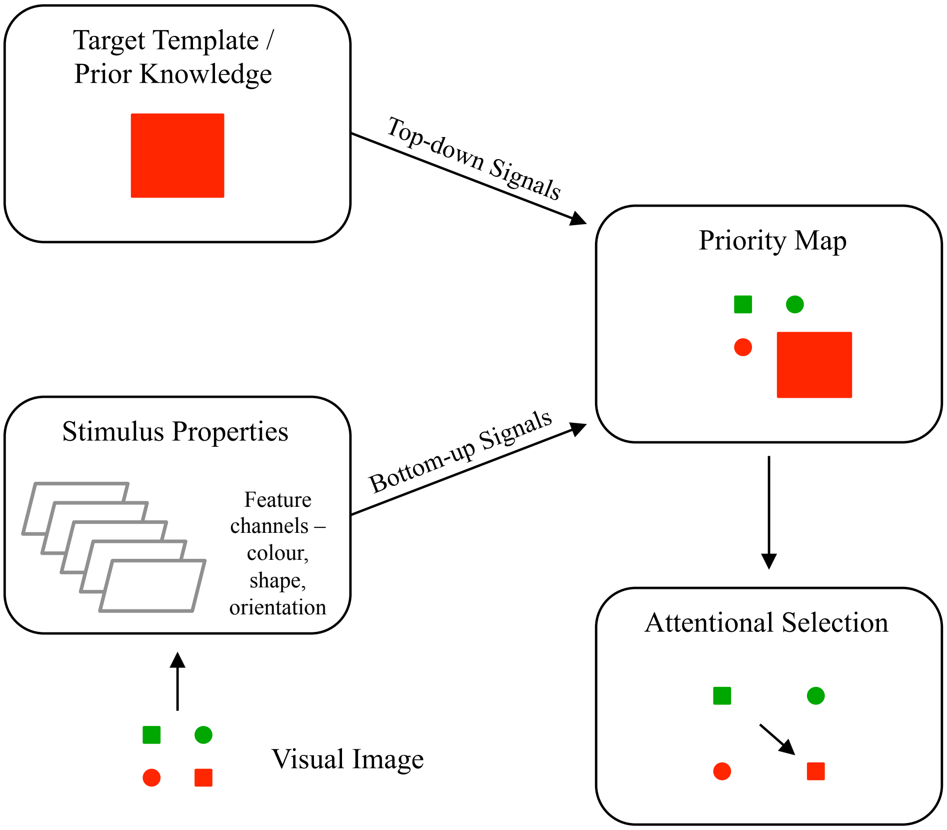

Figure 2. The visual priority map. Illustration of the theoretical visual priority map and its contribution based on models of visual search and visual attention. This map receives input relating to both stimulus-related (bottom-up) and goal-directed (top-down) signals. The stimulus with the highest activation on the priority map (represented by stimulus size in this case) is chosen as the next target of selection. Adapted from Hamker (2006).

delay and subsequently using it to guide behaviour. The memory-guided saccade task requires animals to saccade to a remembered location after holding that target location in working memory for a delay period. Neurons in the PFC showed elevated directional delay period activity during the memory-guided saccade task (Funahashi *et al.* 1989), and also a delayed match to sample task of complex stimuli (Miller *et al.* 1996; see review, Curtis and D'Esposito 2003). These findings demonstrate that the PFC plays a role in the working memory process.

Attention must also be flexibly allocated based on the varying behavioural relevance of a stimulus or task, and the DLPFC has shown to be involved with this as well. Recordings from macaque DLPFC during a non-cued antisaccade switch task (saccade to the location opposite a stimulus) found that neurons in this area modulated their activity depending on whether the monkey was in a prosaccade or antisaccade block, suggesting that neurons in this area maintain some sort of rule selectivity in the flexible control of behaviour (Everling and DeSouza 2005). Also, neuronal encoding of abstract rules has been demonstrated in the PFC while flexibly switching between different rules using complex object stimuli (Wallis *et al.* 2001). Prefrontal activation has also been demonstrated in both macaques and humans on a similar set-shifting task during fMRI (Nakahara *et al.* 2002), and flexibility on a visual discrimination task requires the PFC (Rossi *et al.* 2007, Pessoa *et al.* 2009). Lastly, principal sulcus lesions impaired the maintenance of current rules in working memory during the Wisconsin Card Sorting Task (Buckley *et al.* 2009). Therefore, the DLPFC is an excellent candidate region for influencing a number of processes related to attention, working memory and cognitive flexibility in visual search. In addition to the physiological data of the DLPFC, there have also been studies determining its connections with other areas of the oculomotor network, particularly involving the FEF (Stanton *et al.* 1993), parietal cortex (Petrides & Pandya 1984) and the SC (Fries 1984, Johnston and Everling 2009).

The DLPFC has also been investigated during visual search using neurophysiology and deactivation techniques to determine its role in target selection. Neurophysiological studies in which DLPFC neurons were recorded while monkeys performed visual search tasks (Hasegawa *et al.* 2000, Iba and Sawaguchi 2002, Katsuki and Constantinidis 2012) established that neurons in this area showed activity consistent with the identification of the search target (discriminating the target from distractors), followed by directional delay-period activity (holding target information during the delay). Based on these findings, Iba and Sawaguchi (2002) proposed that the DLPFC forms an attention-memory system, tasked with target identification as well as temporary storage of target information. While the above studies support the role of the DLPFC in visual target selection, a bottom-up feature search task in which the target was defined by colour or shape was used. Deactivation studies using a conjunction search in which the target was defined by shape and colour also showed that muscimol-induced reversible deactivation of the DLPFC resulted in deficits selecting the target from distractors in the contralateral hemisphere (Iba & Sawaguchi 2003). Thus, the DLPFC has been demonstrated to contain visuospatial mnemonic processes, and appears to use this to help correctly identify a target from distractors and subsequently direct attention to the target location. However, its contribution to the searches may have been limited as the target was clearly identified in a feature search, and the target remained constant in the conjunction search therefore removing behavioural flexibility from the task. In addition, the delay following the search required only the target location to be held in working memory, and may not have required temporary retention of any relevant target features. Taken together, these studies suggest that the DLPFC is involved in selective visual attention, possibly working with other areas in the oculomotor network to help provide top-down influence. These studies, however, have not uncovered the potential contribution of the DLPFC when selective visual attention involves working memory or behavioural flexibility.

Given that we now have an understanding of what is occurring at the neuronal level in the oculomotor network (FEF, LIP, SC) during target selection, our goal is to determine what contribution the DLPFC has in flexible or mnemonic processes in target selection. There are multiple approaches that can be taken to determine this contribution, including neuronal recording, stimulation or deactivation. An easy initial step to determine the degree of a brain area's involvement with a particular process is to remove that area and observe the subsequent behaviour. Lesion studies have been invaluable in understanding how the brain works, either naturally in patients or experimentally in animals (e.g. see Fuster 2001). Regarding the link between neurons and behaviour, one method is to permanently or reversibly deactivate a candidate set of neurons and measure any cognitive deficit (Parker and Newsome 1998). One such study did exactly this, which performed PFC lesions and investigated its contribution to visual attention. Monkeys that had unilateral PFC lesions were unaffected in a visual discrimination task involving bottom-up attention or when target identity stayed the same, but showed deficits when the target identity changed frequently across trials (Rossi *et al.* 2007). Though many subdivisions of the PFC were removed, this suggests a role of the PFC in behavioural flexibility (similar to what was noted earlier regarding task switching) and additionally suggests a role in visual attention. While this study examined top-down PFC control processes, these and other cognitive processes still need to be explored in visual search. In addition, while traditional lesion studies have allowed us to gain tremendous knowledge regarding brain function, less permanent and just as effective techniques have been developed to accomplish the same goal.

Cryogenic deactivation is one technique that can be used to reversibly inactivate a brain region or related neural circuit. There are also different methods to cryogenically deactivate the brain. The cryoloop technique involves running chilled methanol through stainless steel loops that are in contact with the cortical surface to selectively and reversibly deactivate a brain area (see review, Lomber *et al.* 1999). By custom designing cryoloops using anatomical MRI data, it is possible deactivate a selected brain area within minutes of running chilled methanol through the loop, and then remove deactivation again within minutes following stoppage of methanol flow. The effect of cortical cooling on neuronal activity has been studied extensively (Jasper *et al.* 1970, Horel 1984, Lomber *et al.* 1996, Lomber *et al.* 1999), and these studies have determined that cooling the cortex below 20°C results in the abolishment of neural activity by means of blocking synaptic transmission. Since the use of various cooling methods (Jasper *et al.* 1970), the use of the highly circumscribed cryoloops have now allowed researchers to chronically and selectively deactivate more specific areas to determine functional specialization (Lomber *et al.* 2010, Hussein *et al.* 2014). Unlike pharmacological inactivation techniques (e.g. muscimol), cryogenic inactivation can be used to both inactivate and reactivate a brain region or circuit within the same task session, collecting control and experimental data within a single session. Though muscimol inactivation has been used to study target selection (Wardak *et al.* 2002, Iba and Sawaguchi 2003), the spread of inactivation can be difficult to replicate and this technique can ultimately result in tissue damage and permanent effects (Lomber 1999). The reproducibility, lack of permanent damage, ability to combine with neuronal recording and amount of control over inactivation makes cooling a useful and effective technique to study the DLPFC and examine its role in visual search.

Although there exists substantial literature which has detailed the neural basis of saccade target selection, some of the cognitive processes related to top-down control in visual search have been less studied. Task-set reconfiguration (behavioural flexibility) and working memory are two cognitive processes that have been linked to the deployment of visual attention, but their roles in visual search have not been identified. Task-set reconfiguration is as follows: when a visual search target changes, the brain must draw upon relevant past knowledge of the goal and target, form a new target template from which to search, reconfigure the top-down selective attention processes, and direct attention by moving the eyes to the new target. Given the theories and evidence discussed thus far, there is logical foundation that these processes—in visual target selection—are associated with the function of the PFC.

The aim of this project is to investigate the role of the DLPFC in top-down cognitive processes related to the deployment of attention as measured in visual search tasks. Specifically, we will reversibly and bilaterally deactivate the DLPFC of rhesus macaque monkeys performing visual search tasks to determine the link between this area and the processes of task-set reconfiguration and working memory, as well as their relationship to selective visual attention. We designed four visual search tasks, with each more cognitively demanding than the previous. The first task was a feature search in which the oddball target was defined by colour. The second task was a constant-target conjunction search, as the target was defined by a combination of shape and colour and the target remained constant for the entire session. Since the target was now perceptually similar to the distractors, top-down control was required to locate the target. The third task was a variable-target conjunction search task, with the search target now changing on a trial-by-trial basis. This task not only required knowledge of the conjunction target, but also tested behavioural flexibility, the process of task-set reconfiguration. The fourth and final task was a variable-target with delay conjunction search task. In addition to requiring knowledge of the target and testing the process of task-set reconfiguration, the trial-specific target must also be held in working memory during the delay before presentation of the array.

We hypothesize that DLPFC deactivation will impair search performance on the visual search tasks involving top-down control and flexible or mnemonic processes. We predict that DLPFC deactivation will result in minimal reaction time or accuracy changes on the feature search task and the constant-target conjunction search task, but that reaction time increases and accuracy decreases will be observed on the tasks involving behavioural flexibility and working memory, the variable-target and variable-target with delay conjunction search tasks.

Materials & Methods

Surgical Procedures

Data were collected from two male rhesus monkeys (*Macaca mulatta*) weighing 9 and 12 kg. All procedures were carried out in accordance with the guidelines of the Canadian Council of Animal Care Policy on the Use of Laboratory Animals and a protocol approved by the Animal Use Subcommittee of the University of Western Ontario Council on Animal Care. Both animals were prepared for chronic implantation of plastic head restraints and stainless steel cryoloops (see Koval *et al.* 2011). Briefly, monkeys underwent an MRI to determine the location and shape of the principal sulcus and subsequently underwent an aseptic surgery. Animals were anesthetized and placed in a stereotaxic apparatus to prepare them for surgery. A craniotomy was performed on each hemisphere to expose the surface of the brain at the principal sulcus. Stainless steel cryoloops (6 × 3 mm) were implanted bilaterally into the caudal portion of the principal sulcus (cPS; see Figure 3) and bilaterally on the cortex immediately dorsal to the principal sulcus (DPC). A plastic head restraint was also implanted, all using dental acrylic. Animals received antibiotics and analgesics post-surgery and were closely monitored by a university veterinarian. Cryoloops were custom fashioned from 23-gauge hypodermic stainless steeling tubing based on the anatomical MR images of the animals. Details and technicalities of the cryoloop—including design, surgery and use—have been previously described (Lomber *et al.* 1999).

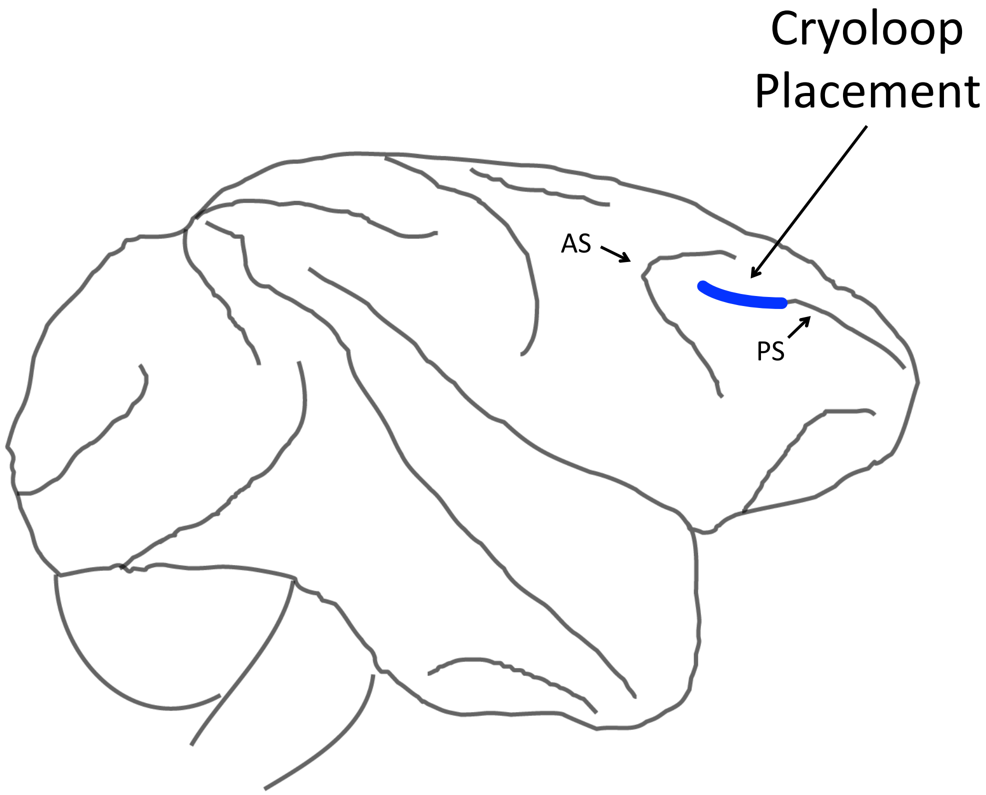

Figure 3. Cryoloop placement in the macaque prefrontal cortex. Cryoloops were implanted bilaterally in the caudal principal sulcus (PS). Blue line denotes approximate location of the cryoloop. AS, arcuate sulcus.

Behavioural Paradigms

Both animals were trained on four visual search tasks in which they were required to make a single saccade to a target stimulus amongst an array of distractors (Figure 4). The first task was a feature search task in which the target was defined by colour. The additional tasks were three versions of a conjunction search task in which the target was identified by both colour and shape. The first of these contained a constant search target. The second task contained a variable search target, and the third conjunction search task consisted of a variable target followed by a delay. All tasks began with the presentation of a central white fixation spot at the center of a CRT monitor. Horizontal and vertical eye positions were recorded at 500 Hz using an Eyelink II system (SR Research, Kanata, Canada).

Feature Search Task

In this task, animals were required to make a saccade to a target defined by colour. Animals were required to fixate on a central white fixation spot (0.5°) and maintain eye position within a 4° x 4° electronic window for 500 msec. Eight visual stimuli (circles approximately 1.3° in size) were then presented 8° equidistant from the fixation (see Figure 4), and monkeys were required to make a single saccade to the search target. The search target was either a green circle with an array of seven red circle distractors, or a red circle with an array of seven green circle distractors. The target was presented pseudorandomly to any of the eight stimuli positions, and thus there were eight conditions for this task. Each session consisted of either a green or a red target and remained constant for each session. On correct trials—there in which the animals fixated at the target location for 200 msec—animals received a liquid reward. Lost or broken fixation at any point during the trial resulted in termination of the trial. Errors were defined as a trial in which the array was presented and the animal made a saccade to one of the distractor stimuli. A two second intertrial interval consisting of a blank screen followed all trials before the next trial commenced.

Constant-Target Conjunction Search Task

In this task, animals were required to make a saccade to a target defined by a conjunction of features, those being colour and shape. The four stimuli were a red square, green square, red circle and a green circle. Thus, on any trial the target shared a common feature, either shape or colour, with the distractors. One distractor had the same shape, one had the same colour, and the other distractor shared no feature. In this task, one of the four stimuli was pseudorandomly chosen as the search target for the each session. To instruct the monkey of which item was the search target for each session, a 50-trial training preview was completed. In this training session, the target began at fixation and subsequently appeared at one of the four target positions following a 500 msec fixation period. This preview allowed the animal to determine what the target was before each session started. In the task, and following a 500 msec fixation of the white fixation spot, the array would be presented and the monkey was required to make a single saccade to the target position. As before, 200 msec fixation at the target location resulted in a correct trial and administration of a liquid reward. Lost or broken fixation at any point during the trial resulted in termination of the trial. Errors were defined as a trial in which the array was presented and the animal made a saccade to one of the distractor stimuli. The target could appear at any of the four locations, with any potential array of distractors. As before, a two second intertrial interval consisting of a blank screen followed each trial before the next trial commenced.

Variable-Target Conjunction Search Task

For the variable-target version of the conjunction search task, the search target was instructed on a trial-by-trial basis. Two of the set of four stimuli—red square, green square, red circle, green circle—were randomly chosen as the search targets in each session, with either of the two being randomly selected as the search target for a particular trial. Following a 500 msec fixation, the target stimulus was presented while the animal maintained fixation. The target stimulus was presented for 500 msec to instruct the monkey of the target for that specific trial (see Figure 4). This was followed by a 100 msec white fixation spot delay to minimize any screen afterimage of the search target, which could serve as a preview to saccade to the target. The array was then presented and the monkey was required to make a single saccade to the target position. As before, 200 msec fixation in the target location resulted in a correct trial and the administration of liquid reward. Lost or broken fixation at any point during the trial resulted in termination of the trial. Errors were defined as a trial in which the array was presented and the animal made a saccade to one of the distractor stimuli. An intertrial interval of two seconds occurred before the next trial commenced.

Variable-Target with Delay Search Task

The final version of the conjunction search task was similar to that of the variable-target version, except with a longer post-target instruction delay. Similar to the variable-target version, two of the four stimuli were randomly chosen as targets for each session, with

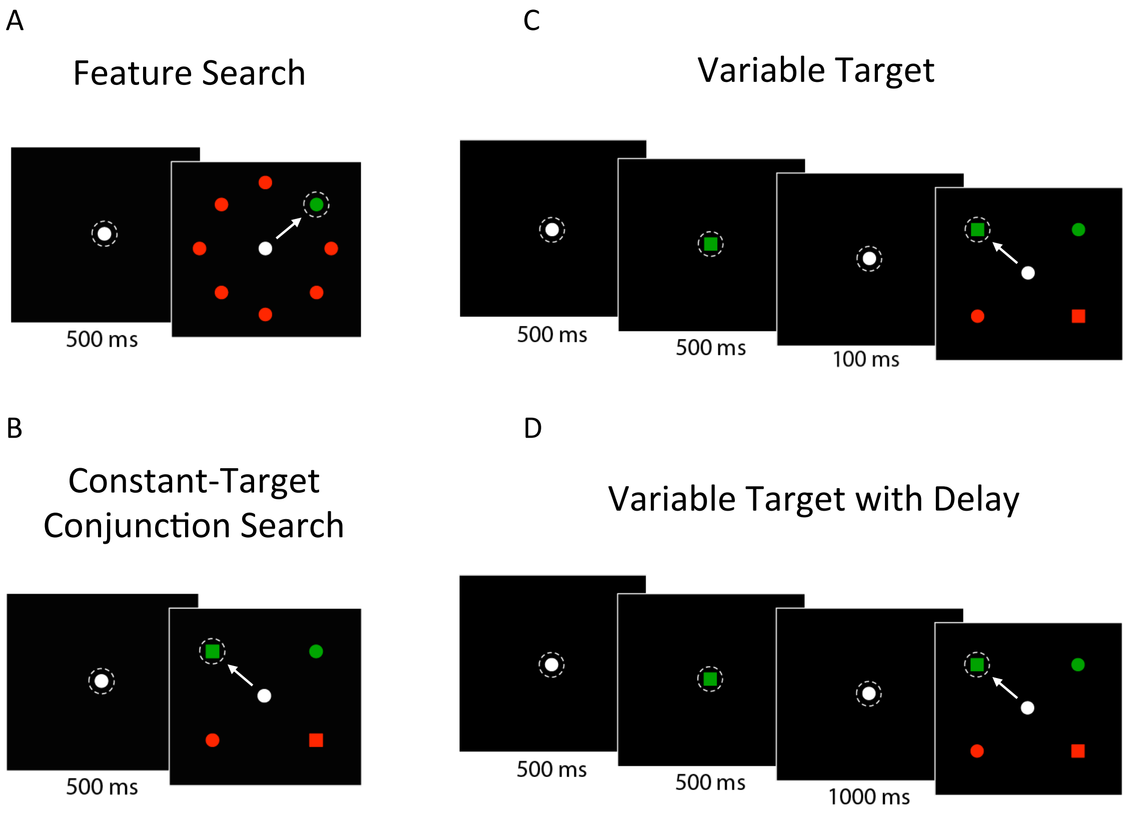

Figure 4. Behavioural search paradigms. (A) In the feature search task, the target was defined by colour (red or green), and randomly appeared in one of eight stimulus positions. (B) Constant-target conjunction search, with any one stimuli being randomly chosen as the target for an entire session. (C) Variable-target conjunction search, with two of the stimuli being randomly chosen for a session, and one of the two stimuli randomly being cued before presentation of the array. (D) Lastly, in the variable-target with delay conjunction search, the task is similar to (C) but included a 1000 msec delay before presentation of the array.

either of the two being randomly selected as a target for a particular trial. Following the 500 msec fixation and a 500 msec target-instruction period, a 1000 msec delay now occurred while the animal maintained fixation. The array was presented at the end of this delay and the monkey had to make a single saccade to the target. As with the previous task, each combination of target and distractor arrays was presented within each session. Again, 200 msec fixation in the target location resulted in a correct trial and the administration of liquid reward. Lost or broken fixation at any point during the trial resulted in termination of the trial. Errors were defined as a trial in which the array was presented and the animal made a saccade to one of the distractor stimuli. A two second intertrial interval occurred before the next trial commenced.

Prefrontal Deactivations

We collected data from a total of 79 sessions, with each animal performing nearly 10 sessions for all four tasks. All data was collected from bilateral deactivation of the cPS loops. The cPS loops have been estimated to deactivate Brodmann areas 46 and 9/46, as well as part of area 8A (Petrides & Pandya 1999, Hussein *et al.* 2014). Since the spread of cooling is approximately 2 mm on either side of the loop, each loop is thought to deactivate the volume of a box with dimensions 10 × 7 × 4 mm, or an estimated 280 mm^3 of cortex. The DPC loops have been estimated to deactivate portions of areas 46, 9, 9/46d and 8 (Hussein *et al.* 2014). Different tasks and/or different search targets were randomly run on separate days, with one session per animal per day.

Both experimental and control data were collected on every day, as each 45 minute session was divided into three 15-minute epochs: pre-cooling, cooling and post-cooling (see Figure 5). An initial 15-minute pre-cooling control epoch was obtained at the beginning of each session. The first three minutes of the epoch were later removed to allow performance to stabilize as the animals were still acquiring the target for that session. At 15 minutes, two pumps were turned on (one for each cryoloop) and methanol drawn up from a reservoir was pumped through Teflon tubing which resided in a methanol bath, the temperature of which was reduced to approximately -80°C by the addition of dry ice (see Figure 6). Chilled methanol then continued to flow through the tubing and through the loop, where after it was then returned to the initial reservoir. Thermocouples attached to the union of the loop monitored the temperature of the loops at all times. Data from the first three minutes of the cooling epoch (15–18 minutes) were excluded as loop temperature was changing, and to allow the animal's performance to reach a steady state at the decreased temperature. Target temperature was approximately 3°C, resulting in a temperature range of between 0–5°C. In majority of sessions (94%), loops were below this target temperature at approximately 18 minutes into the session, with the rest of the sessions reaching this temperature in the next two minutes. At this temperature, a large volume of cortex is deactivated, as ~2 mm of tissue around the loop is deactivated (Lomber *et al.* 1999). At 30 minutes, the two pumps were turned off and chilled methanol stopped flowing through the loops. Temperature rapidly increased back towards normal temperature, with loop temperature going above 30°C within the first minute. Data from the first three minutes of the post-cooling control epoch (30–33 minutes) were excluded as loop temperature was changing, and allow the animal's performance to again reach a steady state at this temperature. Each session was ended at 45 minutes. Following each session, monkeys received liquid until satiation and were returned to their home cages.

Data Analysis

Data was analyzed using custom-designed software in Matlab (Mathworks, Natick, MA). Reaction time was defined as the time between when the array was presented until the time the animal began to make a saccade. Saccade onset was defined as the time when eye velocity exceeded 30°/second. Only the reaction times from correct trials were included in the analysis. Accuracy was calculated as the number of correct trials divided by the total number of trials attempted (saccades to distractors). Following removal of the first three minutes of each epoch, a total of approximately 400 trials were obtained for each session, or 130 trials per session for each epoch. Significance was determined by a one-way repeated measures ANOVA with three levels of factor cooling epoch. The levels were pre-cooling, cooling and post-cooling. An ANOVA was run separately for each animal and each task, for both saccadic reaction time and accuracy. For example, a one-way repeated measures ANOVA was run for *Monkey B's* reaction time for feature search task. Three data sets were included in the ANOVA; pre-cooling epoch reaction time, cooling epoch reaction time, and a post-cooling epoch reaction time. Accuracy was calculated for each session, and then averaged across the sessions. In contrast, the saccadic reaction times were pooled across all sessions for each epoch. For example, if there were 130 trials per session in each epoch, and ten sessions, there would 1300 saccadic reaction times in each epoch for the ANOVA. Follow-up tests (one-tailed two sample student *t* tests) were performed given a significant ANOVA. One test was between pre-cooling and cooling epochs, and another test was between cooling and post-cooling epochs to determine where the significance resided.

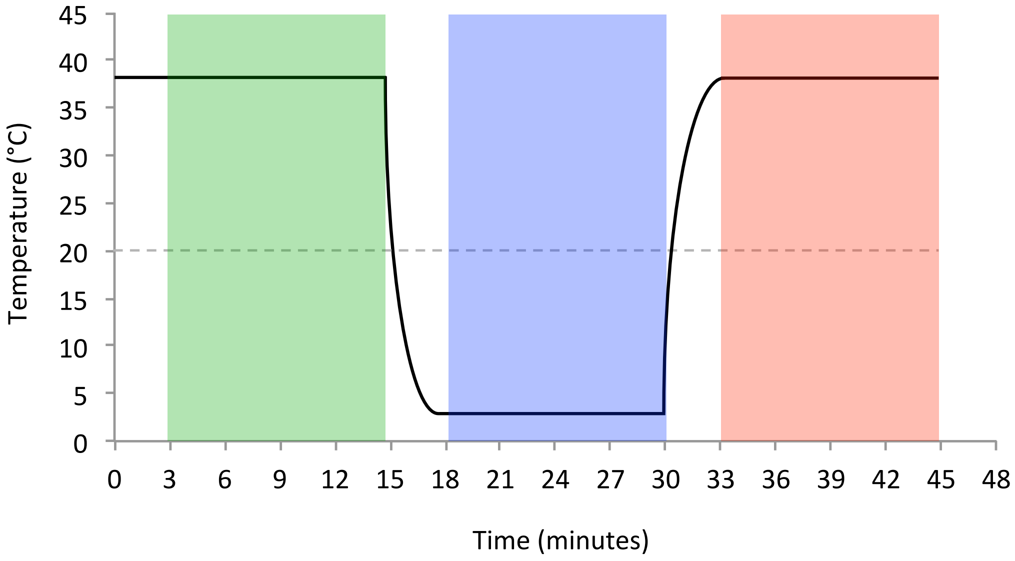

Figure 5. Cortical cooling timeline. Each 45-minute session was divided into three epochs: pre-cooling, cooling and post-cooling. The first three minutes of each epoch were removed to allow performance to reach a steady state. Solid line indicates cryoloop temperature. Dashed line indicates temperature at which synaptic transmission is abolished (20 °C).

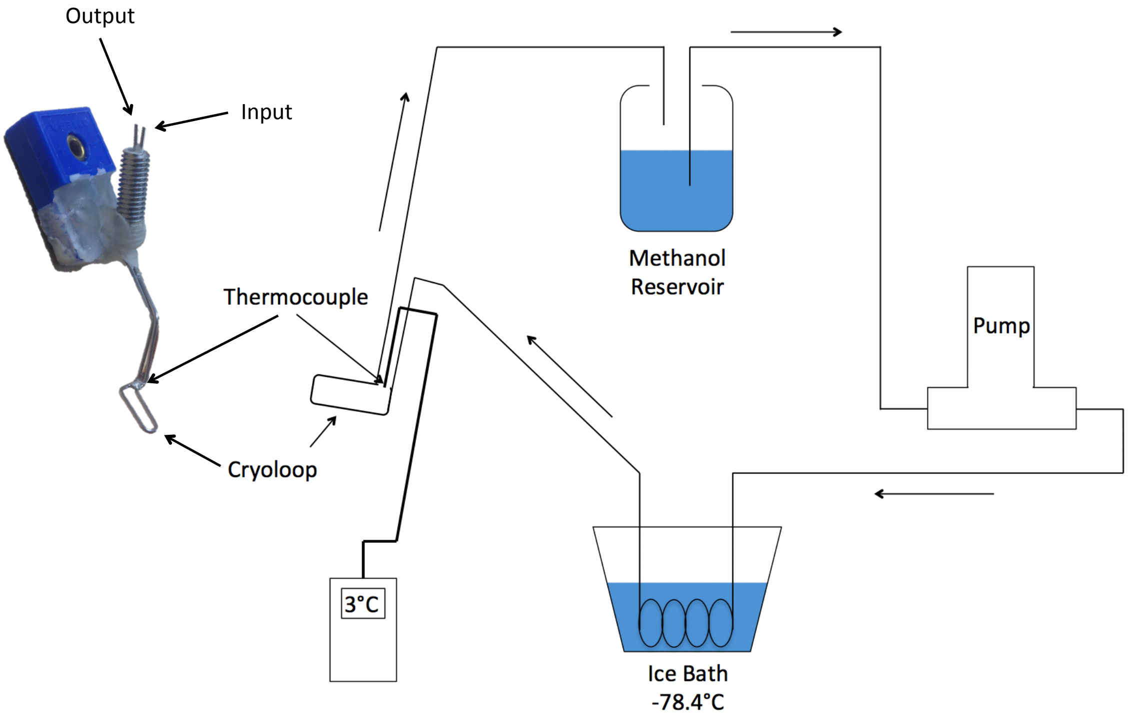

Figure 6. Reversible cryogenic deactivation with cryoloop (left) and experimental cooling setup (right). Room-temperature methanol was pumped from a reservoir through Teflon tubing which passed through a methanol dry ice bath that was cooled to approximately -80°C. The chilled methanol was then pumped through the cryoloop and back to the reservoir. Cryoloop temperature was monitored at all times by an attached thermocouple, with the temperature reading out to a thermometer. Temperature was maintained around the 3°C by adjusting the flow rate of the pump.

Results

Effects of DLPFC deactivation on feature search task performance

Figure 7 shows each monkey's performance on the feature search task (n = 10 sessions for *Monkey B* consisting of n = 5028 total trials, and n = 10 sessions for *Monkey T* consisting of n = 4982 total trials). Each session was divided into three epochs; pre-cooling, cooling and post-cooling. Accuracy is represented as proportion correct responses. Saccadic reaction times for each animal are also plotted in msec. Bilateral cooling of the cPS resulted in performance changes for both animals. To statistically examine effects on accuracy, a one-way repeated measures ANOVA was performed and showed no change in accuracy across the different epochs for both *Monkey B* and *Monkey T* ($F(1,2) = 2.78$, $p = 0.119$ for *Monkey B*, $F(1,2) = 1.38$, $p = 0.277$ for *Monkey T*). *Monkey B* showed a significant effect for reaction time ($F(1,2) = 80.28$, $p < 0.001$), as did *Monkey T* ($F(1,2) = 13.58$, $p < 0.001$). Post-hoc comparisons (one-tailed two sample t tests) revealed that *Monkey B* had an increase in reaction time during the cooling epoch compared to both the pre-cooling epoch ($p < 0.001$) and the post-cooling epoch ($p < 0.001$). Post-hoc comparisons for *Monkey T* revealed this difference was not significant between the pre-cooling and cooling epochs ($p = 0.053$), but was significant between the cooling and post-cooling epochs ($p < 0.001$). *Monkey B* reaction time increased to 202 msec during cooling from 185 msec before, and then dropped to 196 msec following cooling. The reaction time change for *Monkey T* changed from 206 msec during cooling to 198 msec following cooling (see Table 1).

Effects of DLPFC deactivation on constant-target conjunction search task performance

Figure 8 shows each monkey's performance on the constant-target conjunction search task (n = 10 sessions for *Monkey B* consisting of, n = 3827 total trials, and n = 9 session for *Monkey T* consisting of n = 3828). A one-way repeated measures ANOVA showed that bilateral cooling of the cPS resulted in no change in accuracy either monkey ($F(1,2) = 1.47$, $p = 0.256$ for *Monkey B*, $F(1,2) = 2.21$, $p = 0.142$ for *Monkey T*). Regarding reaction time, *Monkey B* showed a significant effect ($F(1,2) = 160.37$, $p = < 0.001$). *Monkey T* also demonstrated a change in reaction time during this task ($F(1,2) = 31.62$, $p = < 0.001$). Post-hoc comparisons for *Monkey B* (one-tailed two sample t tests) revealed that a reaction time increase occurred between pre-cooling and cooling ($p < 0.001$), as well as reaction time decrease between cooling and post-cooling ($p < 0.001$). Post-hoc comparisons for *Monkey T* revealed that there was a decrease in reaction time between the pre-cooling and cooling epoch ($p < 0.001$), which then decreased again following cooling ($p < 0.001$). *Monkey B* had a reaction time increase from 199 msec during pre-cooling to 230 msec during cooling. This decreased back to 201 msec during the post-cooling epoch. *Monkey T*'s reaction time seemed to decrease as the session progressed. Starting with a 224 msec reaction time during the pre-cooling epoch, this decreased to 215 msec during the cooling epoch, and decreased again during the post-cooling epoch to 207 msec.

Effects of DLPFC deactivation on variable-target conjunction search task performance

Figure 9 shows each monkey's performance on the variable-target conjunction search task (n = 10 sessions for *Monkey B* consisting of n = 3872 total trials, and n = 10 sessions for *Monkey T* consisting of $n = 3680$ total trials). cPS deactivation affected performance in both animals when the target now changed on a trial-by-trial basis. A one-way repeated measures ANOVA demonstrated *Monkey B* had a change in accuracy during cooling ($F(1,2) = 6.99$, $p = 0.006$), whereas *Monkey T* had no change in accuracy ($F(1,2) = 1.60$, $p = 0.229$). Post-hoc comparisons (one-tailed two sample student t tests) revealed that *Monkey B* had a decrease in accuracy between both the pre-cooling and cooling epochs ($p = 0.009$) and an increase between the cooling and post-cooling epochs ($p = 0.026$). After performing at 86% during pre-cooling, *Monkey B*'s accuracy dropped to 77% during cooling. This drop however showed recovery, with accuracy increasing back to 83% in the post-cooling epoch. Both animals also showed a statistically significant effect on reaction time during the cooling ($F(1,2) = 206.05$, $p = < 0.001$ for *Monkey B*, $F(1,2) = 21.26$, $p = < 0.001$ for *Monkey T*). Post-hoc comparisons for *Monkey B* demonstrated an increase in reaction time during cooling compared to pre-cooling ($p < 0.001$), which then decreased when comparing cooling to post-cooling ($p < 0.001$). *Monkey T* also demonstrated a reaction time increase, increasing from pre-cooling to cooling ($p < 0.001$), and demonstrated a decrease between the cooling and post-cooling epoch ($p < 0.001$). *Monkey B* demonstrated a reaction time increase from 223 msec during pre-cooling, to 255 msec during the cooling epoch, which then decreased to 238 msec following cooling. *Monkey T* had a reaction time increase to 218 msec during cooling, compared to 208 msec during the pre-cooling epoch and 210 msec during the post-cooling epoch.

Effects of DLPFC deactivation on variable-target with delay conjunction search task performance

Figure 10 shows each monkey's performance on the variable target with delay search task (*n* = 10 sessions for *Monkey B* consisting of *n* = 3540 total trials, and *n* = 10 sessions for *Monkey T* consisting of *n* = 3084 total trials). Again, to statistically evaluate both animal's performance, a one-way repeated measures ANOVA showed that cooling had a significant effect on *Monkey B*'s accuracy ($F(1,2) = 5.14$, $p = 0.017$). A repeated measures ANOVA revealed that *Monkey T* demonstrated no change in accuracy during cooling ($F(1,2) = 2.71$, $p = 0.094$). Post-hoc comparisons (one-tailed two sample student *t* tests) revealed a decrease in accuracy when comparing the pre-cooling to the cooling epoch ($p = 0.009$) and comparing the cooling to the post-cooling epoch ($p = 0.008$). Performing at 82% during pre-cooling, *Monkey B*'s accuracy dropped to 70% during cooling of the cPS. This accuracy increased back to 82% in the post-cooling epoch. A one-way repeated measures ANOVA revealed both animals showed an effect on saccadic reaction time ($F(1,2) = 88.82$, $p < 0.001$ for *Monkey B*, $F(1,2) = 17.92$, $p < 0.001$ for *Monkey T*). Reaction time effects for *Monkey B* increased during cooling compared to pre-cooling ($p < 0.001$), and subsequently decrease when comparing the cooling and post-cooling epoch ($p < 0.001$). Post-hoc comparisons also revealed *Monkey T* had a significant increase in reaction time when comparing the pre-cooling and cooling epochs ($p < 0.001$) as well as between cooling and post-cooling ($p < 0.001$). *Monkey B* had a reaction time increase from 224 msec during pre-cooling to 256 msec during cooling. Reaction time decreased to 236 during the post-cooling epoch. Reaction time for *Monkey*

T increased during cooling to 209 msec from 199 msec during pre-cooling, which then decreased back to 199 msec following cooling.

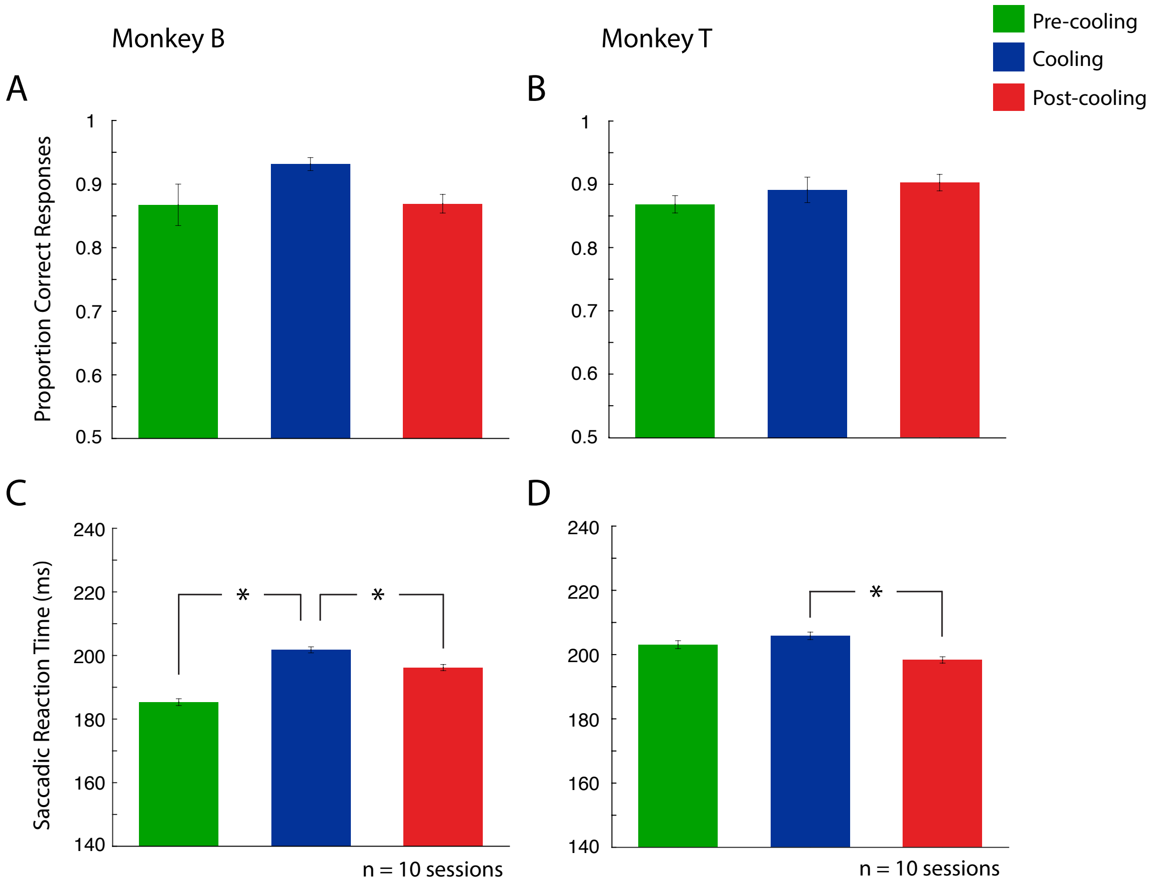

Figure 7. Performance on the feature search task. Left column (A and C) represents *Monkey B*, while right column (B and D) represents *Monkey T*. A and B denote proportion correct responses. C and D denote saccadic reaction time. Error bars indicate SEM. See legend for pre-cooling, cooling and post-cooling epochs. * $p < 0.05$.

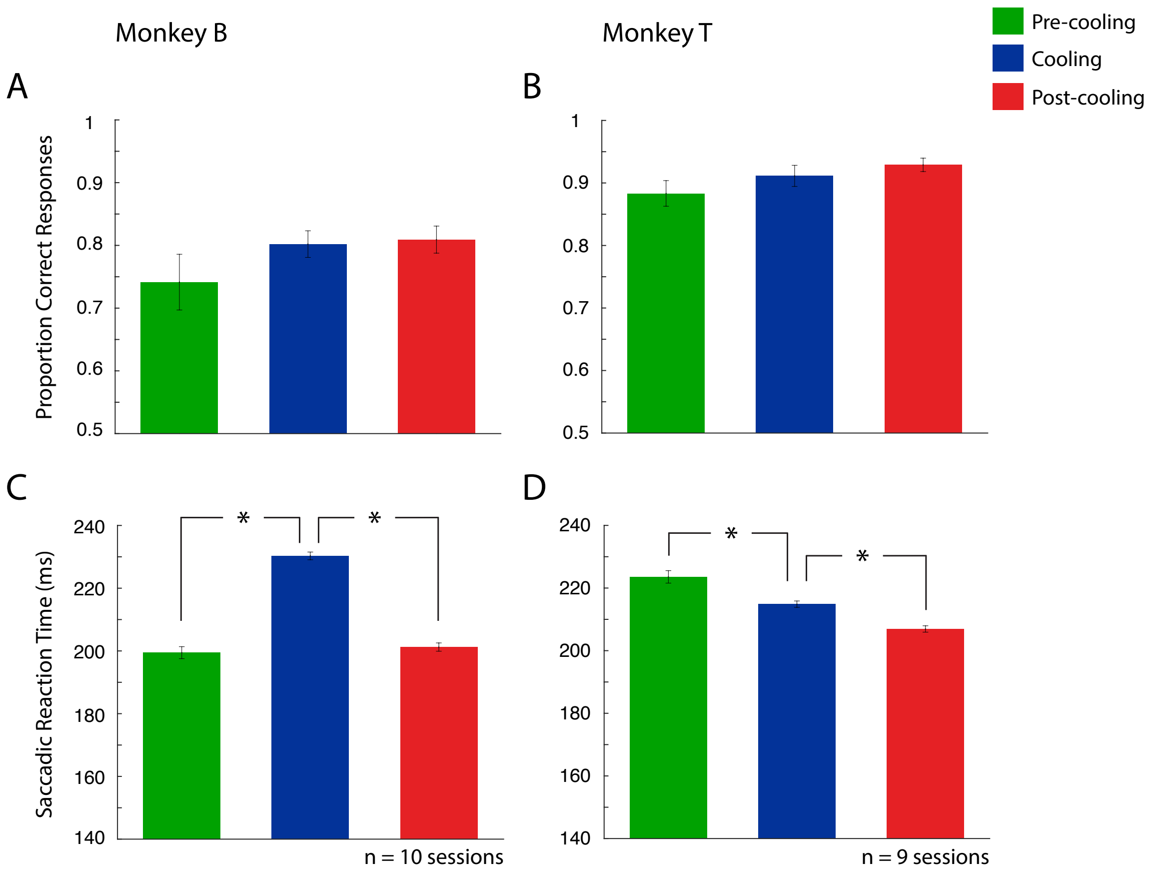

Figure 8. Performance on the constant-target conjunction search task. Left column (A and C) represents *Monkey B*, while right column (B and D) represents *Monkey T*. A and B denote proportion correct responses. C and D denote saccadic reaction time. Error bars indicate SEM. See legend for pre-cooling, cooling and post-cooling epochs. * $p < 0.05$.

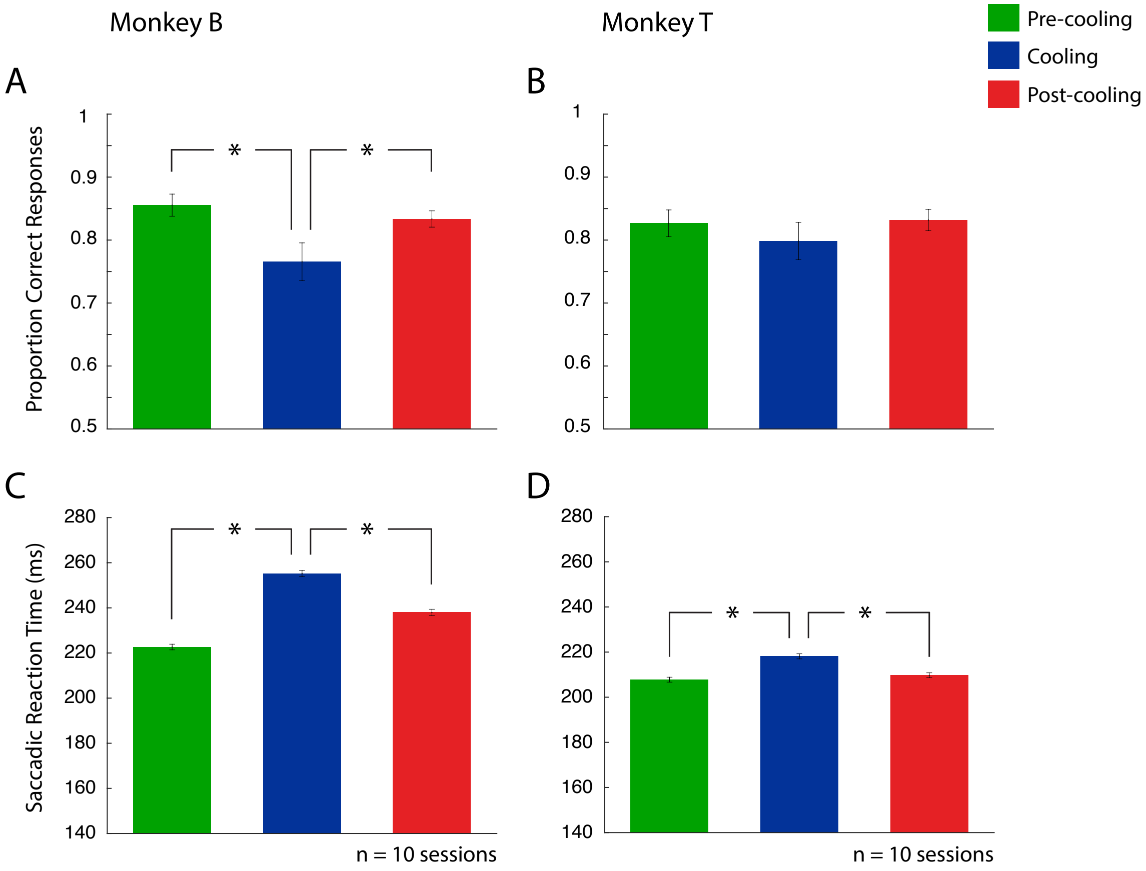

Figure 9. Performance on the variable-target conjunction search task. Left column (A and C) represents *Monkey B*, while right column (B and D) represents *Monkey T*. A and B denote proportion correct responses. C and D denote saccadic reaction time. Error bars indicate SEM. See legend for pre-cooling, cooling and post-cooling epochs. * $p < 0.05$.

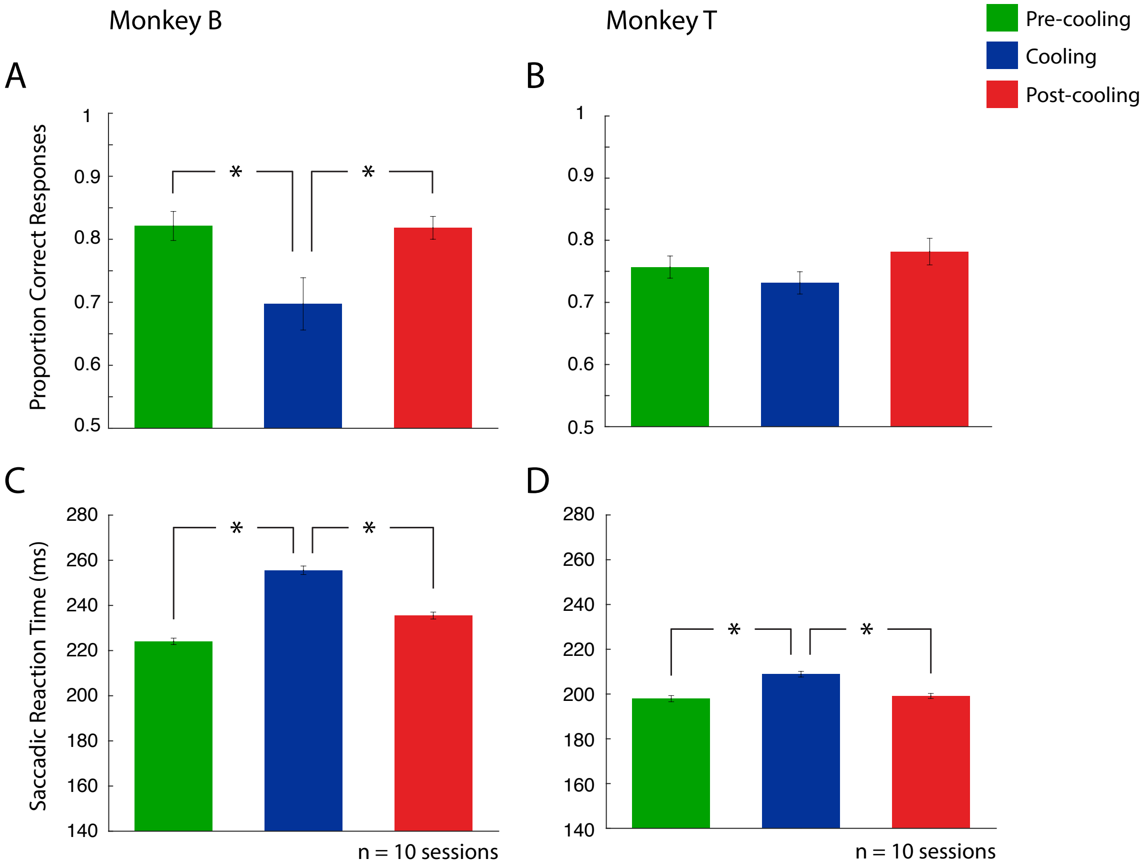

Figure 10. Performance on the variable-target with delay conjunction search task. Left column (A and C) represents *Monkey B*, while right column (B and D) represents *Monkey T*. A and B denote proportion correct responses. C and D denote saccadic reaction time. Error bars indicate SEM. See legend for pre-cooling, cooling and post-cooling epochs. * $p < 0.05$.

Table 1. Accuracy and reaction time in a visual search tasks. Accuracy (in proportion correct) and reaction time (in msec) for both *Monkey B* and *Monkey T* in the feature search task, constant-target conjunction search task, variable-target conjunction search task and the variable-target with delay conjunction search task.

Search Task	**Monkey B**						**Monkey T**					
	Accuracy (%)			**Reaction Time (msec)**			**Accuracy (%)**			**Reaction Time (msec)**		
	Pre	Cool	Post	Pre	Cool	Post	Pre	Cool	Post	Pre	Cool	Post
Feature	86.7	93.2	86.9	185	202	196	86.8	89.1	90.3	203	206	198
Constant-target conjunction	74.1	80.2	80.9	199	230	201	88.3	91.1	92.9	224	215	207
Variable-target conjunction	85.6	76.6	83.4	223	255	238	82.7	79.9	83.2	208	218	210
Variable-target with delay conjunction	82.1	69.8	81.8	224	256	236	75.7	73.1	78.2	199	209	199

Discussion

Our findings confirm and extend the DLPFC involvement with the deployment of attention, specifically when it involves behavioural flexibility and/or working memory. Performance deficits on a number of visual search tasks were seen when the region lining the caudal principal sulcus of the DLPFC was reversibly deactivated in two rhesus monkeys. Although we observed some performance changes during cooling for feature and constant-target conjunction search tasks, this was inconsistent between the two animals. One animal showed increased reaction time for both tasks, while the other showed an incomplete reaction time increase for the feature search, and decreased reaction time over the progression of the constant-target conjunction search task. We did however, observe more consistent effects of increased reaction time in one animal, and increased reaction time with decreased accuracy in the other for the variable-target and variable-target with delay conjunction search tasks—the more demanding tasks. These results suggest that DLPFC involvement is most critical for situations requiring more cognitive control, as greater and more consistent effects appeared during the more cognitively demanding tasks.

Upon cooling the DLPFC, we noted behavioural performance changes in all four of our visual search tasks. Both animals demonstrated an increase in saccadic reaction time during cooling for the feature search, though for *Monkey T* this was only between the cooling and post-cooling epochs. For the constant-target conjunction search, while both monkeys showed reaction time changes, neither showed a change in accuracy. *Monkey B* showed an increase in reaction time during cooling, whereas *Monkey T* showed a decrease in reaction time as the session progressed. As for the variable-target conjunction search task, both animals demonstrated an increase in reaction time during the cooling epoch, whereas *Monkey B* additionally demonstrated an accuracy decrease. Lastly, the variable-target with delay conjunction search task revealed performance deficits as well. Though only *Monkey B* showed an accuracy decrease during cooling, both animals showed an increase in saccadic reaction time. While deactivation of the DLPFC led to minor impairments on the first two tasks, each monkey demonstrated greater impairments in the last two tasks. Altogether, the most consistent effects were seen in tasks that required behavioural flexibility, and behavioural flexibility with working memory.

The concept of a visual salience or priority map has been proposed to account for neural activity that is consistent with representing all competing stimuli in our visual field, and which is crucial in order to direct attention to the correct object of a scene (Wolfe 1994, Desimone and Duncan 1995, Bundesen *et al.* 2005, Fecteau and Munoz 2006, Hamker 2006). By assigning each stimulus an attentional weight, combining both bottom-up (salience) and top-down (relevance) factors, the stimulus with the highest activation on the priority map can be chosen. Bottom-up attentional processing is thought to consist of distinct feature channels, with each feature (such as colour, shape or orientation) of a stimulus activating an individual channel (Wolfe 1994, Itti and Koch 2001, Hamker 2006). Thus, a red circle would activate both the feature channel “red”, and the feature channel “circle”. These feature channels would then be combined back together to represent this stimulus on the priority map. Top-down attention can also bias the signals on the priority map, or perhaps earlier on the feature channels. By searching for a specific target (e.g. a red circle amongst an array of coloured circles and squares), top-down control can enhance or filter select feature channels to help increase the activation of the target on the priority map (Wolfe 1994, Hamker 2006, Woodman *et al.* 2013), making it possible to identify a target that is perceptually similar to the distractors around it. Top-down attention also involves the use of a target template. The target template is a representation of the target (either defined by its features, or a picture-like representation), which can be used to aid visual search (Desimone and Duncan 1995, Bundesen *et al.* 2005, Hamker 2006, Woodman *et al.* 2007, Woodman *et al.* 2013). When looking from one stimulus to the next, the template, which is thought to be held in working memory (Vickery *et al.* 2005, Woodman and Chun 2006, Woodman and Luck 2007, Olivers 2009, Woodman *et al.* 2013), can also serve to send feedforward signals and resolve the winner on the priority map (Hamker 2006). By examining the model of the priority map in the context of visual search, it can provide a framework and shed light on the role the PFC plays in the deployment of attention.

One of the reasons we tended to see greater effects during the final search task (variable-target with delay conjunction search task) was that each task was more cognitively demanding than the previous. Beginning with the feature search, the target stood out from the distractors because there was only a single feature discriminating the target, that being colour. Little top-down control was necessary to direct attention to the singleton, as the target's activation on the priority map would have been higher than the other stimuli (Wolfe 1998, Fecteau and Munoz 2006). The oddball stimulus draws our attention by way of bottom-up processes, as the target is unique and highly salient compared to the stimuli around it. For example, the set size effect is not seen for simpler visual search tasks in which the target has a unique feature (Treisman and Gelade 1980, Wolfe 1994, Findlay and Gilchrist 2003). The set size effect refers to the increase in reaction time that accompanies the increase in the number of stimuli or distractors (the set size) in a visual search task (Palmer 1994, McPeek *et al.* 1999, Jerde *et al.* 2011). This effect is not seen for simple tasks, as distinguishing the target in a feature search is an automatic process using bottom-up attention, with search time not increasing when the number of distractors increase.

In the constant-target conjunction search task, the target was defined by a conjunction of features, shape and colour. Some of the distractors now shared a feature with the search target. One distractor was the same shape, one distractor was the same colour as the target, and the third distractor was of a different shape and colour. Thus, the target was now more similar to the distractors compared to the feature search. Searching for a target defined by a conjunction of features results in a less efficient search as it is more difficult to discriminate the target from the distractors, and where attention now needs to be directed by way of top-down processes to the target (Treisman and Gelade 1980, Wolfe 1998, Woodman *et al.* 2007, Woodman *et al.* 2013). For example, if the target was a green square, the subject must look for stimuli that are green and stimuli that are square. Since the target no longer stands out, its activation on the priority map from bottom-up processes would be similar to the distractors. Top-down activation of the colour green and square shapes (or filtering of the colour red and circle shapes), would make the green square target the most salient stimulus as it contains both features, and attention could subsequently be directed to this target (Treisman and Sato 1990, Wolfe 1998, Fecteau and Munoz 2006). This is indeed the case, as FEF neuronal activity in a conjunction search reflects that the target stimulus has the highest activation, followed by stimuli with the same colour, stimuli with the same shape, and finally stimuli that share no feature with the target (Bichot and Schall 1999a). Behavioural data support this as well, with errant saccades reflecting stimulus activation going to distractors with the same colour or same shape, and then to distractors sharing no feature with the target.

The next two search tasks, the variable-target and variable-target with delay conjunction search tasks were more cognitively demanding than the first two tasks, and more consistent performance deficits were seen in our two animals during cooling. For the variable-target conjunction search task, an update must be made on a trial-by-trial basis of what to search for. This flexible control process or task-set reconfiguration updated the target template for each trial (Desimone and Duncan 1995, Bundesen *et al.* 2005, Vickery *et al.* 2005, Woodman *et al.* 2013). The feature channels that were filtered before (colour, shape, etc.) were now dynamically reconfigured for each new search target, with the PFC likely taking responsibility for this process (Di Lollo *et al.* 2001, Itti and Koch 2001). This flexibility allowed the animal to perform the same task but direct attention to the new target. As well, what was the target on the previous trial could now have been a distractor on the current trial. This task required more cognitive control, as evidence has been shown that targets on a previous day's session maintain a higher than normal neuronal representation on the priority map (Bichot and Schall 1999a, Schall 2002), let alone stimuli that were targets on the previous trial. Repetition of target or target features for even a few trials has also been shown to both decrease reaction time and increase accuracy, demonstrating the increased attentional demand with a variable target paradigm (Bichot and Schall 2002). This task-set reconfiguration must now truly operate on a trial-by-trial basis, using top-down control to filter out the appropriate distractors.

The final paradigm was the variable-target with delay conjunction search task. Besides task-set reconfiguration and the guidance of attention to the conjunction search target, the DLPFC was now tasked with holding a mnemonic representation of the target or target features (the target template) in working memory during the delay period. The delay-period activity of neurons in this area demonstrate that this area plays some role in working memory during visual search, possibly maintaining a mnemonic representation of the target template (Hasegawa *et al.* 2000, Sawaguchi and Iba 2002). The new target on a trial-by-trial basis required temporary maintenance of the updated target template followed by the correct filtering of appropriate distractors. In summary, after examining each of our tasks, these results suggest that the more demanding the task, the greater the involvement of the DLPFC, and the greater the effects seen during DLPFC cooling.

A study similar to the present one had previously suggested that the PFC was important when attention was to be flexibly allocated based on the behavioural relevance, or, by using top-down control. Rossi and colleagues (2007) performed lateral PFC lesions of the right hemisphere in macaques (removing the FEF, DLPFC, ventrolateral PFC, and frontopolar cortex) and found that their behavioural deficits on a visual discrimination task increased in magnitude the more frequently the target changed. This suggested that the top-down reconfiguration process was performed by the PFC, lending support to previous proposals (Di Lollo *et al.* 2001, Itti and Koch 2001). Although important findings, there were several differences between the study by Rossi and colleagues and the present one. The researchers had only narrowed this attentional process to the lateral prefrontal cortex as a whole as they performed lesions on these animals. Utilizing the technique of reversible cryogenic deactivation, we were able to narrow the possible location of task-set reconfiguration to the DLPFC, specifically the region lining the cPS. In addition, Rossi and colleagues studied covert attention and did not use a conventional visual search task. The task in which they used was a visual discrimination task, as the animals were required to discriminate the orientation of a line. The task was completed not with a saccade, but with the monkeys performing a bar release while maintaining central fixation throughout the task. Although they removed eye movements from this task to isolate the reconfiguration process, overt attention is a crucial component of directing attention to objects of interest (Findlay and Gilchrist 2003). A similar research group (Pessoa *et al.* 2009, Rossi *et al.* 2009) also performed the same orientation discrimination task using functional neuroimaging on human subjects. They found higher activation in the middle frontal gyrus (MFG, the approximate area of deactivation in our study) during a target switch than when the target remained the same, and also found higher activation during a more cognitively-demanding colour-cued task than a colour pop-out task. These findings are in line with ours regarding the relationship between attentional demands and top-down control by the PFC. For the present study, we further pinpointed the DLPFC as responsible for the attentional reconfiguration process in visual search, with the addition of a working memory component as well.

Additional human research has also implicated the DLPFC for similar processes to the ones studied here, as there have been a number of studies investigating the link between working memory and visual search. In order to determine if these processes use the same limited-capacity processing system, a task involving both should interfere with each other. Performing a visual search task at the same time as a working memory task is known as the dual-task paradigm (Woodman *et al.* 2001). According to the logic of this paradigm, if both processes compete for same processing resources, filling visual working memory should interfere with visual search. Woodman and colleagues (2007) had human subjects perform a dual-task paradigm, with a visual search task during the delay of a working memory task. Their results were similar to the findings of Rossi and colleagues (2007; who in contrast removed the lateral PFC from monkeys), in that the two tasks interfered with each other when the search target changed on a trial-by-trial basis, but subjects were not impaired when the target remained constant across trials. Woodman and colleagues suggested that since the flexible control required in the attention-shifting visual search task and the working memory task interfered with each other, these processes might compete for the same resources and even have the same underlying anatomical locations. Support for this hypothesis comes from more recent findings. fMRI data (Makino *et al.* 2004, Anderson *et al.* 2010) found overlapping brain regions for both visual search and working memory. By testing subjects on a dual-task paradigm, Anderson and colleagues (2010) localized increased activation again to the MFG. This activation was greater than that of the same area for a working memory task or a visual search task by itself, suggesting that the greater the attentional demand, the greater the involvement of the DLPFC for top down control, consistent with our results (Also Iba and Sawaguchi 2002, Rossi *et al.* 2009).

While we were not expecting any effects during the cognitively less-demanding feature and constant-target conjunction searches, studies in this area have shown mixed findings which could shed light on the lack of consistency between our two animals. Regarding feature search, application of theta TMS to disrupt the DLPFC in humans determined that this area was involved in conjunction search where the target was defined by colour and orientation, but not for feature search where the target was defined only by colour (Kalla *et al.* 2009). This supports the idea of bottom-up attentional processes in the feature search task, and top-down control for conjunction targets. Neuronal recordings from the PFC also suggest that this area is more involved with top-down processes than bottom-up processes in visual search (Buschman and Miller 2007). Katsuki and Constantinidis (2012), however, showed that neurons in the DLPFC are involved in bottom-up searches, as these neurons discriminated simple targets from distractors in a feature search for colour. In addition, this discrimination occurs on a similar timescale to other areas in the oculomotor network (FEF, SC, LIP). Based on these findings, they proposed that the DLPFC is also part of this network, and furthermore contributes to the formation of a priority map. They also suggested that the identification of targets from distractors occurs in parallel, as the DLPFC detects the targets just as quickly as area LIP of the parietal cortex, an area thought of as contributing more to bottom-up attention (Buschman and Miller 2007). This data contradicts that of Kalla and colleagues (2009) by suggesting that the DLPFC is actually in fact involved in feature search tasks. Monkeys performing a feature search pop-out task in an MRI scanner also support lateral PFC activation during the simpler bottom-up feature searches (Wardak *et al.* 2010).

Regarding conjunction search in which a target is defined by a conjunction of features, it has been suggested that when target identity remains constant it may be not as challenging to identify the target, and that the PFC may be minimally involved. Similar to their previous study (Woodman *et al.* 2001), Woodman and colleagues (2007) showed that even when working memory was filled to capacity, dual-task visual search remained efficient as long as the target remained constant. This finding supports views of automaticity by Logan (1990, 1992) that following an initial performance stage of acquiring and directing attention to a target in visual search, attentional shifts thereafter could be quickly guided by a target template in long-term memory (Woodman and Chun 2006, Woodman *et al.* 2007, Woodman *et al.* 2013). Short-term memory templates allow us to maintain limited-capacity temporary information and use it for the task at hand. Long-term memory on the other hand is of unlimited capacity utilizing different brain regions from working memory, and target templates from a vast number of stimuli could be retrieved whenever they were needed to guide attention (Woodman *et al.* 2013). This automaticity would now allow the DLPFC to operate in a more minimalistic manner similar to its possible role in the feature search task. Evidence supporting the contribution of long-term memory comes from FEF recordings showing targets that were targets in the previous had higher than normal representation as distractors on the current session (Bichot and Schall 1999a, Schall 2002). Studies using EEG event related potentials have shown that activity consistent with holding a template in working memory decreased in amplitude the longer the repetition of a target, and this was accompanied by both an increase in amplitude of the ERP long-term memory measure and a concurrent decrease in reaction time (Carlisle *et al.* 2011, Woodman *et al.* 2013). This supports the role of automaticity (Logan 1990) in that long-term memory retrieval is quick and automatic. Though the target template could be stored in long-term memory, some theories still posit that the PFC retrieves these representations for directing attention to the target (Woodman and Chun 2006, Olivers 2009). The literature seems to show mixed findings on constant-target conjunction searches, and our data reflects this as well. The automaticity theory could explain *Monkey T*'s performance on the constant-target conjunction search, as his reaction time decreased over the course of the session is similar to human findings

(Carlisle *et al.* 2011). At the beginning of the constant-target conjunction search task, *Monkey T* would still be acquiring the target for that particular session. After some time, the target stimulus would be clearly known and a target template in long-term memory would serve as a template to help direct attention to the target. Thus, cooling the cPS would show no performance effects, similar to what we observed.

On tasks in which the target changes frequently, the target template must be continuously updated to represent the currently relevant stimulus, and then maintained in working memory during search (Desimone and Duncan 1995, Di Lollo *et al.* 2001, Bundesen *et al.* 2005, Vickery *et al.* 2005, Woodman and Chun 2006, Rossi *et al.* 2007, Woodman *et al.* 2007, Woodman *et al.* 2013). This flexible control process (task-set reconfiguration) is thought to generate a new target template to search for on each trial, making a variable-target search more cognitively demanding than a constant-target conjunction search. The PFC is thought to be responsible for this reconfiguration process (Rossi *et al.* 2009), which is in line with extensive research concluding the PFC as responsible for maintaining relevant information and using it to direct top-down attention. Task-relevant information has been shown to be held in the DLPFC by using a cued target-detection task (Kadohisa *et al.* 2015), and principal sulcus lesions impaired the maintenance of current rules in working memory during the Wisconsin Card Sorting Task (Buckley *et al.* 2009). Also, an n-back task (a task in which subjects must compare the current stimulus to the stimulus presented either 1, 2 or 3 trials previous) using geometric designs demonstrated DLPFC activation responsible for both working memory and manipulation of targets (Ragland *et al.* 2002). This activation was greater for maintenance and manipulation than for either process alone, similar to the current theme of more cognitive demand, more DLPFC involvement. An additional hypothesis is that several target templates can be actively held in long-term memory, and individual templates can be directly accessed to hold in working memory for the current trial (Oberauer 2002, Olivers 2009). This would mean the two targets for any session could be available for direct access, and the current target could be placed in working memory for attentional selection, or maintained until array presentation. DLPFC cooling could affect the retrieval of the target template, the maintenance, or both. If cooling affected maintenance, performance effects would be seen with a longer delay requiring target template maintenance. However, if cooling only affected retrieval, similar effects would be seen for any variable target task, since target template retrieval from long-term memory would be required in situations with no delay or a long delay. Our results suggest cooling would affect retrieval since similar effects were seen for both variable-target searches.

One result that requires further probing is the finding of increased reaction time during deactivation, which can be explored by examining the neural mechanism of target selection. This increase could be due to one of two factors in visual search; either delayed target selection or delayed saccade generation, or possibly even both (see Figure 11). The delay of target selection could be a longer discrimination time, which is the time it takes to discriminate the target from the distractors. At the neuronal level (in the oculomotor network and inferotemporal cortex), this is reflected by the time at which the activity for the target differs significantly from the distractor activity, based on a target compared to a distractor in the response field (Desimone 1998, Sato *et al.* 2001, Schall 2002). The activity for a target is enhanced, whereas the activity for a distractor is attenuated, thus activity is biased to the behaviourally relevant stimulus (Desimone and Duncan 1995, Chelazzi *et al.* 1998, Desimone 1998, Schall 2002). It is hypothesized that top-down control from the prefrontal cortex could be modulating these neuron's activity (e.g. see Desimone 1998, Miller and Cohen 2001). DLPFC cooling could potentially disrupt these modulation signals, thus delaying the identification of the target, delaying the discrimination time and ultimately delaying the onset of saccade. The reaction time increase could also be accounted for by a delayed or a slower rate of rise of neural activity up to the saccade initiation threshold (see Figure 11). Though analysis of saccade parameters during principal sulcus cooling showed slight differences in velocity, duration and gain (Koval *et al.* 2011), these differences would still allow the animal to properly respond to the task by selecting the target with a saccade. As well, although bilateral cooling of the DLPFC during prosaccades to a stimulus resulted in no reaction time increase (Hussein *et al.* 2014), there may be a differing effect on target selection. If cooling the DLPFC did result in a delay of saccade generation, this would be the same for all tasks, and the feature search (which uses the least top-down control) would show a baseline reaction time increase. The saccadic reaction time increases for both monkeys are the smallest on the feature search task, with the more demanding tasks showing larger reaction time increases during cooling. Thus, if cooling results in a slight reaction time increase due to delayed saccade generation, the more demanding tasks still show an even greater reaction time increase, suggesting that cooling is affecting the discrimination of the target from the distractors. Support for the idea that cooling affects discrimination time also comes from constant-target conjunction search performance from *Monkey T*. The decrease in reaction time over the course of the session suggests that the decrease in reaction time from pre-cooling to cooling does not affect saccade generation and result in longer reaction times. Although this reaction time again decreases into the post-cooling period, it seems as if DLPFC cooling did not affect *Monkey T* at this task. While the explanations of what is causing the increased reaction times may seem plausible, further investigation with neurophysiology is required.

Given the evidence that the DLPFC is suggested to play a role in the attentional or mnemonic processes in visual search, there is a good chance that this area communicates or plays some role with the oculomotor network in target selection. As the other areas of this network are evidenced to play a role in forming a priority map of the visual world (Schall 2002, Thomas & Pare 2007, Shen et al. 2011), it is not known what the DLPFC contributes to this network. The findings by Katsuki and Constantinidis (2012) demonstrated that the DLPFC identifies target stimuli from distractors on a similar timescale as other areas of this network. Neuroimaging studies have also identified this area as part of the frontoparietal attention network, responsible for eye movements, directing attention and stimulus salience (Corbetta *et al.* 1998, Corbetta and Shulman 2011). How the DLPFC exerts its action during visual search or communicates with other brain areas during target selection is not known. The DLPFC could be responsible for top-down feedforward signals to extrastriate visual areas and possibly activating or filtering feature channels (colour, shape, orientation, etc; Miller *et al.* 1996, Wolfe 1998). It could also be involved with signaling the areas of the oculomotor network to either enhance or filter stimuli directly on the priority map (Wolfe 1994, Bundesen *et al.* 2005, Hamker 2006), which would then make it easier to determine the target from other stimuli in the visual field. One of the ways in which we could help determine the underlying neuronal effects of cooling would be to deactivate the cPS while recording from another area in the oculomotor network. Evidence from the pro- and antisaccade task during

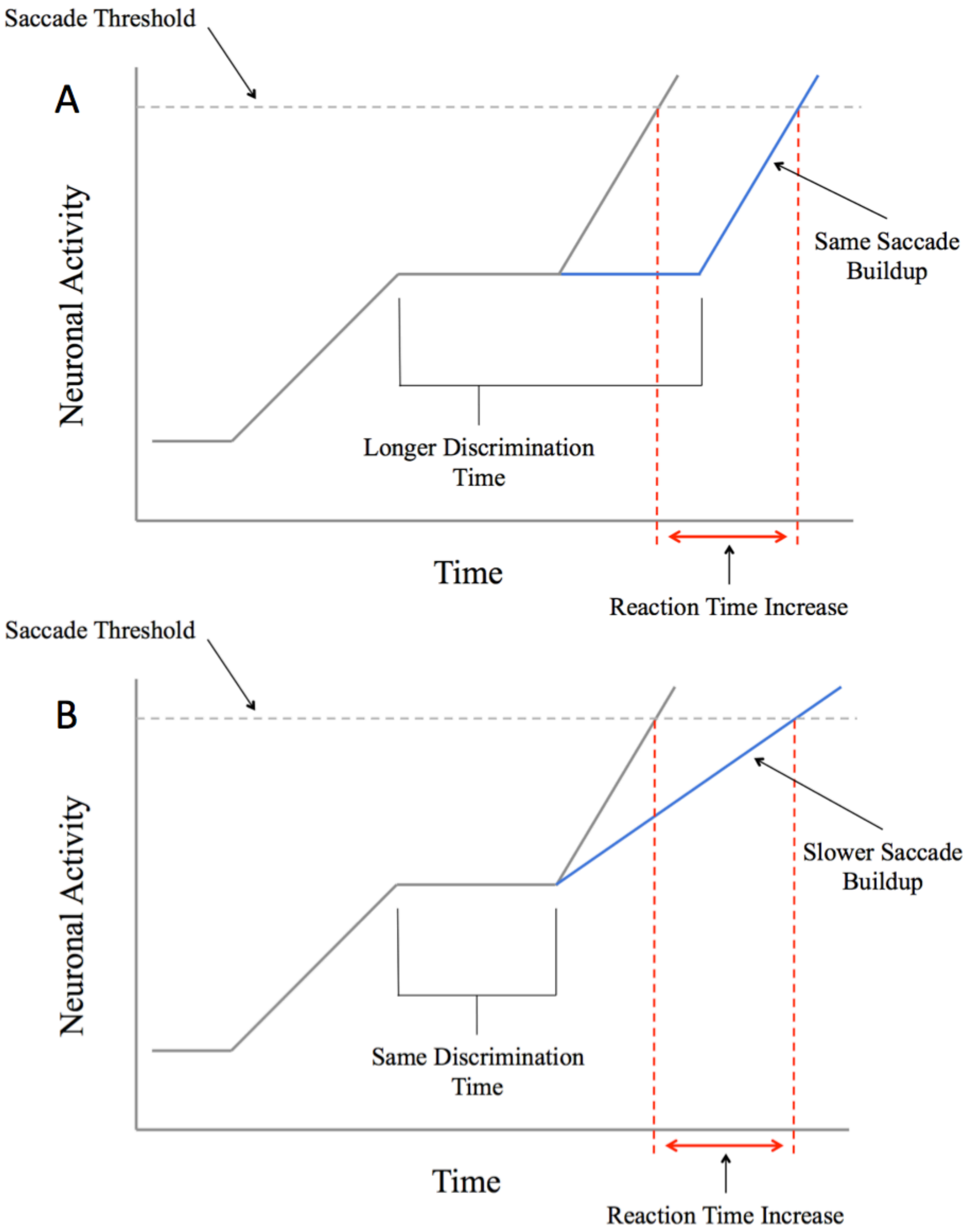

Figure 11. Possible mechanisms of increased saccadic reaction time during cooling. (A) Solid grey line denotes neuronal activity in oculomotor network, increasing until saccade threshold is reached and saccade is executed. Blue line denotes possible activity during DLPFC cooling. Time begins at array presentation. A longer discrimination time to identify the target from the distractors could result in a reaction time increase, even with unaltered saccade buildup rate. (B) Target discrimination could require the same time, but cooling could reduce the rate of saccade buildup to threshold.

DLPFC cooling and simultaneous neuronal recording demonstrated that cooling the DLPFC alters activity in at least one area of the oculomotor network, the SC (Koval *et al.* 2011, Johnston *et al.* 2014). Specifically, unilateral cooling resulted in changes in pre-stimulus and stimulus-related activity, as well as saccade-related activity while affecting reaction times. DLPFC deactivation has also been shown to affect neuronal activity in inferotemporal cortex during a delayed match-to-sample task (Fuster *et al.* 1985) and the parietal cortex during memory-guided saccades (Chafee and Goldman-Rakic 2000). FEF, SC or LIP neuronal recording during cPS cooling would be necessary to determine what neural activity changes occur for target selection in visual search. This could determine if these areas take longer to identify the target—longer discrimination time—or if the target is identified as usual but saccade buildup rate is longer during PFC cooling.

It is reasonable to assume that the DLPFC is responsible for spatial and motor mapping, whereas the ventrolateral PFC (VLPFC) is more devoted to features and object information (Hamker 2006). This idea can be explained by the way in which visual information is processed. Since there are two main streams of visual processing, consisting of a dorsal "where" stream through the parietal cortex for spatial and location processing, and a ventral "what" stream through the temporal cortex for feature-based processing (Mishkin and Ungerleider 1982), it might be expected that they converge in the PFC to integrate this information for planning and execution. Though it has been long shown that neurons in the PFC demonstrate activity consistent with working memory, the potential segregation between object-based and location-based working memory has been an issue of contention (e.g. Itti and Koch 2001, Hamker 2006). Neurons recorded in the primate frontal cortex initially supported this segregation, finding mnemonic object activity more ventrally and mnemonic location activity more dorsally (Wilson *et al.* 1993). As well, Courtney and colleagues (1996) used positron emission tomography (PET) imaging to determine object working memory increased blood flow more in inferior frontal cortex, whereas superior frontal blood flow increased for location working memory. Although these studies found segregation of the two streams, it could have reflected the segregation of two types of working memory in the tasks. A task designed to test both object and location working memory was used to probe the integration of the two streams in the PFC, and neurophysiology showed the integration of these two streams in the lateral PFC, as neurons showing both object and location delay activity were spread out equally between the dorsal and ventral lateral PFC (Rao *et al.* 1997). A high level of integration has been demonstrated between dorsal frontoparietal network and the ventral frontoparietal network, with the dorsal network being responsible for goal-directed target selection, whereas the ventral network is more responsible for working with the dorsal PFC to orient attention to unexpected salient stimuli (Corbetta and Shulman 2002). In our study, cooling the cPS deactivates the more ventral portion of the DLPFC. The final task integrates both object and spatial attention, as the variable-target with delay conjunction search requires the animal to hold a mnemonic representation of the target during a delay and subsequently locate and direct attention to the target stimulus amongst other distractors. It might be beneficial to deactivate different subregions of the lateral PFC, cooling more dorsally or more ventrally from the principal sulcus to increase the area of deactivation, and see what effect a more dorsal or more ventral deactivation area would have on performance in our paradigms.

Manipulation of our paradigms to further affect attentional demand in addition to working memory and flexible control is one potential next step. As previously described, the set size effect is a great tool to determine the difficulty of a paradigm, by plotting the number of stimuli against reaction time (Wolfe 1994, Wolfe 1998, Jerde *et al.* 2011). Comparing the slopes of pre-cooling and post-cooling against cooling would give us an understanding of the cognitive demand of the task, and be able to see if the reaction time slope increased, signifying the increased difficulty to identify the target (Woodman *et al.* 2007). Increasing the number of distractors in the conjunction searches would create a more cognitively demanding task, as there are more distractors that need to be filtered before a target can be identified. Though our set size is four in all conjunction search tasks, we could potentially add more distractors to make a more demanding task, and explore for a set size effect.

Speed-accuracy tradeoff was another point of potential discussion, as both reaction time and accuracy were measured in this study. A speed-accuracy tradeoff is when the subject has some sense that they are impaired, and thus compensate by slowing down their responses in order to ensure their accuracy is not diminished, while actually getting better at the task. Though we did not find this with our performance, there seemed to be a trend toward increased reaction time and increased accuracy in the feature search and constant-target conjunction search task performance. Had there been both an increase in reaction time and an increase in accuracy, one possible explanation to this finding could have been looking at the competitive accumulator model (similar to biased competition), present in attentional selection tasks (Desimone 1998, Usher and McClelland 2001). This model of the neural mechanisms of selection proposes that there are multiple populations of neurons integrating incoming sensory information about the choice stimuli, and through reciprocal competition, the population with the greatest activity ultimately wins and the stimuli represented by that population is chosen. Cooling could potentially disrupt the signals needed for target identification, thereby allowing more time for the population identifying the target to get the greatest activity and be the next item of selection, thus being more accurate (see Shen *et al.* 2010). So, though this may look like a speed-accuracy tradeoff, the increased reaction time is a result of disrupted signals, and the increase in accuracy would be a potential consequence based on this mechanistic model. Though not seen in our results, this model could explain a speed-accuracy tradeoff in a target selection paradigm.

Examining reaction time and accuracy data, baseline performance was somewhat different between the four tasks at the time of data collection. It may have been beneficial to gather behavioural data when the animals were performing similar on each task, as the fact that our animals were well trained on all of the tasks suggests that they had already achieved ceiling performance. With similar baseline performance during cooling, a more accurate comparison between tasks could have been made. In addition, the lack of significance of accuracy for *Monkey T* on the variable-target and variable-target with delay conjunction search tasks could be an issue of power. Though *Monkey B* showed an accuracy decrease in both those tasks, *Monkey T* only showed a trend, slightly in the variable-target conjunction search task and more so in the final task that included the delay. More sessions may give us a better estimation of the mean and make any potential differences statistically reliable to match with *Monkey B*. Finally, while we have designed four visual search paradigms, additional tasks can be designed. A more attention-demanding task to potentially see reaction time and accuracy effects in both monkeys would be a variable-target conjunction search task with a variable delay as well. The same delay on each trial might allow a more routine approach to completing the task, and more focused attention may be required to complete a variable-target and variable-delay conjunction search task. A longer delay would also increase the cognitive demand, as the target template would have to be maintained longer in working memory (Schmidt and Zelinsky 2011).

The results of the present study suggest that the DLPFC is involved in visual search, specifically to attentional processes related to behavioural flexibility and working memory in visual search. However, the DLPFC may be minimally involved on simple, searches involving bottom-up processes and become more activated when the attentional demands of the task are increased, such as when top-down reconfiguration for a new search target is required, temporary retention of a search target is necessary, or both of the above. The fact that the more demanding tasks involve behavioral flexibility and working memory, these two processes could be competing for the same cortical processing resources in the DLPFC, resulting in performance deficits during deactivation in visual search. Exactly what effects DLPFC deactivation has for outgoing neural signals or on the rest of the oculomotor network will require further probing, specifically single-unit recording of other network areas during DLPFC cooling on visual search tasks.

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