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Chapter 12

The role of lateral orbitofrontal cortex in the inhibitory control of emotion

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12.1. **Introduction**

The prefrontal cortex (PFC) governs the executive control of information processing and behavioral expression, including the ability to selectively attend and maintain information, inhibit irrelevant stimuli and impulses, and evaluate and select the appropriate response (Knight *et al.* 1995, Miller and Cohen 2001). This cognitive and behavioral control facilitates successful achievement of complex goal-directed behaviors. Some evidence suggests that all regions of the PFC (dorsal, ventral, lateral, medial) have the capacity to perform the same type of executive control functions (i.e. evaluate, maintain, inhibit, or select) [(Duncan and Owen 2000)]. However, other evidence indicates that particular regions of the PFC are biased toward specific functions and information domains (Shimamura 2000, Muller *et al.* 2002).

In particular, evidence indicates that the orbitofrontal cortex (OFC) participates in the executive control of information processing and behavioral expression by inhibiting neural activity associated with irrelevant, unwanted, or uncomfortable (e.g. painful) information, sensations, or actions (Shimamura 2000). The role of the OFC in inhibition has gained increasing prominence in the literature due to the dramatic rise in research investigating the neural correlates of social and emotional processing. Most investigations of social or emotional processing reveal that the OFC is involved; however, the exact role that it plays is still debated. Here, we review evidence that the lateral OFC, extending to the ventrolateral PFC, facilitates successful goal-oriented behavior by inhibiting the influence of emotional information in the context of physical sensation, selective attention, emotion regulation, judgement and decision-making and social relationships.

12.2. **The mechanism of inhibition**

Inhibition is the process of suppressing or restraining an action, sensation, feeling, thought, or desire. It is a general mechanism that is employed over many different types of stimuli and behavior. Inhibition is usually volitional, such as consciously suppressing the impulse to yell at a bad driver on the road or the desire to eat a piece of chocolate cake when you are on a diet. However, inhibition can also occur automatically, such as the suppression of neural activity that happens without full conscious awareness. For example, this automatic suppression can be observed in the decrease in neural response to the second sensory stimulus in a rapid sequence of stimuli. This automatic suppression or "gating" of sensory information regulates the amount of information that the organism receives at one time, thereby facilitating the ability to process and organize that information efficiently (Adler *et al* 1982, Freedman *et al*. 1996, Knight *et al*. 1989, Waldo and Freedman 1986). Data suggests that both volitional and automatic inhibition involve the interaction of "top-down" inhibitory control mechanisms originating from orbitofrontal, and other prefrontal areas, and 'bottom-up' sensory and stimuli based properties represented in primary sensory (e.g. V1, V2, somatosensory, etc.) and association (e.g. inferior temporal lobe for visual objects) cortex (Knight *et al*. 1989).

Several proposed theories provide a framework for understanding the role of the OFC in inhibition. The Dynamic Filtering Theory proposes that the prefrontal cortex, as a whole, operates as a dynamic filtering mechanism for the multitude of incoming sensory information by maintaining selected neural activations and inhibiting (or "filtering") others (Shimamura 2000). According to this view, different regions of the PFC govern different domains of information, with the OFC providing a dynamic filter for affective information [as opposed to cognitive information which is governed by lateral PFC (Shimamura 2000)].

The Disruption Theory, on the other hand, proposes that negative affect is received as an "alarm signal," which automatically instigates a conscious, evaluative process of that negative situation or stimulus. This evaluation inhibits (or "disrupts") negative affect through orbital- and ventral PFC-mediated "top-down" neural projections that suppress neural activity associated with negative affect (Eisenberger and Lieberman 2004, Lieberman *et al.* 2004). Other theoretical frameworks emphasize a broader role for the OFC in the inhibition as well as the integration of emotional information on behavior (Bechara *et al*. 2000). Here, we consider recent research using multiple experimental paradigms in light of these theoretical frameworks.

12.3. **OFC anatomy**

In order to exert inhibitory influence, the OFC must receive information about sensory stimuli in the internal (e.g. physical sensations) and external environment. After monitoring this incoming information, the OFC uses its neural projections to suppress the neural activity associated with that stimuli in order to regulate its impact on the organism's behavior. The anatomy of the OFC is particularly suited for this function. The OFC receives neural inputs from every sensory modality—olfactory, gustatory, vision, auditory, and somatosensory—and is ideally suited to monitor information from multiple sources. In addition, the OFC has direct projections to the primary and secondary sensory cortices, and can modulate the strength of the neural signal coming from that sensory cortex, regulating the influence of that sensory signal on the rest of the brain, and, ultimately, on behavior (Barbas 2002, Kringelbach and Rolls 2004).

In addition to its reciprocal connections to primary and secondary sensory cortices, the OFC has immense reciprocal connections with subcortical structures, such as the amygdala, thalamus, and periaquaductal gray area, that are central in emotion processing, and thus has the perfect architecture for modulating neural activity associated with affective information and affectively motivated behavior (Barbas 2002, Kringelbach and Rolls 2004).

The best evidence for the functional use of this neural architecture in inhibitory control is a dynamic relationship between neural structures in which increased activity in the OFC is specifically related to decreased activity in the neural region where that stimulus is represented. In this chapter, we review evidence for such a dynamic relationship.

For ease of discussion in the chapter, we will refer to the region shown in red as the dorsolateral PFC (DLPFC) [BA 9, 46], green as the medial PFC (MPFC) [BA 8], purple as the ventral medial PFC (VMPFC) [BA 25, 32], turquoise as the ventrolateral PFC (VLPFC) [BA 44, 45, 47], light blue as the medial OFC (BA 11, 12) and navy blue as the lateral OFC (BA 47, 11).

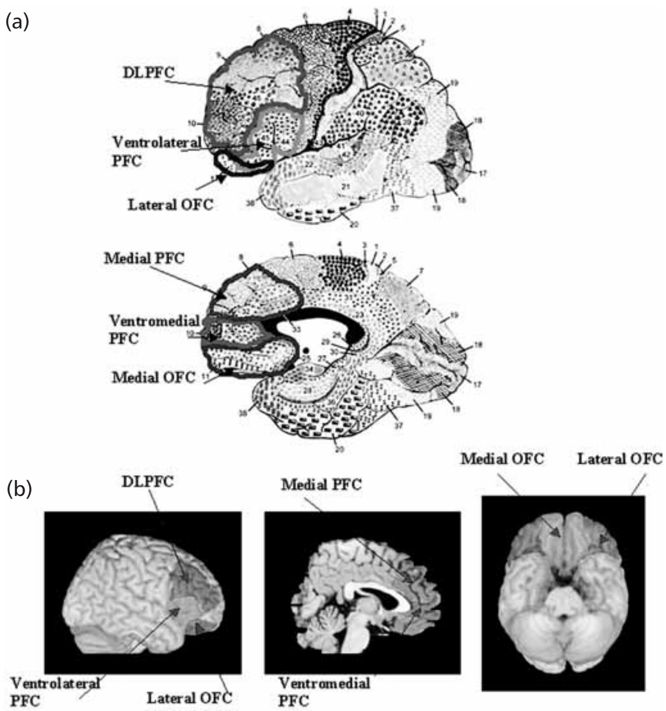

Fig.12.1 (a). It shows original Brodmann map colorized to highlight different Brodmann areas as well as basic prefrontal regions. 1(b) shows basic prefrontal regions on a canonical brain. Area shown in red is DLPFC, in pink is ventrolateral PFC, in purple is ventromedial PFC, in green is medial PFC, in light blue is medial OFC, and in dark blue is lateral OFC. See Plate Section in the color gallery.

Source: 12.1(a) adapted from Mark Dubin (http:// spot.colorado.edu/~dubin/talks/brodmann).

12.4. **Regulation of sensation**

Data from multiple sources illustrate that the OFC suppresses neural activity related to aversive or painful sensations. Rule *et al.* (2002) investigated neurophysiological response to unpredictable, mildly aversive sensory events in healthy adults, DLPFC lesion patients and OFC lesion patients (Rule *et al.* 2002, Shimamura 2000). Scalp event-related potentials were recorded while subjects received mild shocks to the wrist (i.e. somatosensory stimuli) or heard loud bursts of noise while watching a silent movie. For both the somatosensory and the auditory conditions the OFC patients showed enhanced neural activity, observed as larger P300 amplitude, in response to the sensory stimuli, when compared to the DLPFC group as well as healthy controls. Interestingly, the DLPFC lesion patients had reduced ERP responses to the sensory stimuli, a finding that has been demonstrated before and suggests that the DLPFC is important for the maintenance, or "up-regulation," of sensory stimuli.

Additionally, both the DLPFC and healthy control participants showed habituation of neural responding, reflected in decreasing P300 amplitudes, at later presentations of the aversive somatosensory stimuli. In contrast, for the OFC lesion patients, neural response remained exaggerated over successive trials and did not habituate (Rule *et al.* 2002). The process of habituation facilitates goal-oriented behavior by enhancing attention to novel stimuli in the environment, subsequently allowing attentional resources to be re-allocated once initial processing of the stimuli has been accomplished. If habituation does not occur, the person may become overwhelmed with sensory input and have a difficult time allocating attentional and neural resources to other tasks. This increased neural noise in the system can lead to impaired attention as well as greater interference of non-relevant information, ultimately leading to reduced memory capacity and a disruption in goal-oriented behavior.

This enhanced neural responding to both auditory and somatosensory stimuli occurred 300 ms after the onset of the stimulus and was observed most robustly at the Pz electrode. This component (i.e. the P300) most likely reflects neural activity from the temporo-parietal junction (TPJ) a region of multimodal association cortex (Soltani and

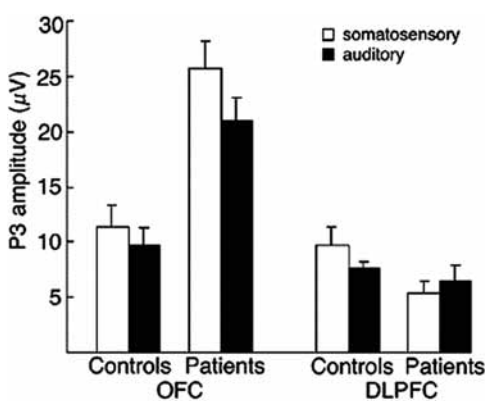

Fig 12.2. It shows mean P3 amplitude to somatosensory and auditory stimuli for orbitofrontal cortex (OFC) patients and controls and for dorsolateral prefrontal (DLPFC) patients and controls. As compared with other groups, the OFC patients exhibit grossly disinhi\bited P3 responses.

Source: Taken from Rule, Shimamura *et al.* (2002) with permission from Psychonomic Society Publications.

Knight 2000). However, enhanced neural response in the OFC patients was also observed at posterior frontal electrodes (Fz) 150 ms after the somatosensory stimulus (i.e. the N150). These data suggest that the OFC normally inhibits aversive sensations very early in sensory processing by regulating neural activity in posterior sensory association areas. Interestingly, OFC lesion patients have normal posterior P300 amplitudes in nonemotional tasks (Hartikainen *et al*. 2000b), suggesting that, consistent with the Dynamic Filtering Theory, the OFC specifically regulates automatic processing of emotional and/or aversive information.

A subsequent study measured multiple types of emotional and physiological response, including heart rate, skin conductance, and facial expression, when OFC patients received a surprise loud burst of noise in an unanticipated startle task (Roberts *et al*. 2004). OFC lesion patients displayed more surprise behavior and reported more fear than the normal controls in response to the noise. This disinhibition of behavior is consistent with the idea that the OFC may act as a filtering system to aversive sensory inputs such as an acoustic startle.

12.5. **Suppression and modulation of pain**

The ability to suppress the neural activity in response to physical sensation is most important if that physical sensation is painful. Acute and chronic pain can be highly disruptive to people's lives and an immense amount of research effort is devoted to understanding components of pain treatment, especially the effects of placebo, since placebo treatment can lead to pain relief without damaging side effects (Harden 2005, Wager 2005). Multiple studies investigating the effect of placebo treatment on pain show evidence of a dynamic interaction such that increased lateral OFC/VLPFC activity is related to a decrease in neural activity in neural regions associated with the origin of the painful sensation, which is then related to a decrease in self-reported pain symptoms (Lieberman *et al*. 2004, Petrovic and Ingvar 2002, Petrovic *et al*. 2002, Wager *et al*. 2004). For example, Lieberman *et al*. (2004) tested chronic pain patients pre- and post-placebo treatment. They found that the dorsal ACC, a region associated with the affective component of pain symptoms, decreased between pre- and post-testing, whereas right VLPFC activity increased between pre- and post-treatment. Importantly, at post-treatment, right VLPFC activity was negatively correlated with dorsal ACC activity and positively correlated with symptom improvement. The authors interpret these results as consistent with Disruption Theory and suggest that the right VLPFC mediates a conscious, cognitive evaluation and expectation associated with placebo (i.e. "I am getting treatment, so my pain symptoms will not be as bad") and these expectations suppress activity in pain associated brain regions. Wager *et al*. (2004), shows evidence consistent with this idea. They show that increased neural activity in the lateral OFC (bilaterally) and DLPFC (bilaterally) during anticipation of pain predict less pain related activity in the thalamus, insula and dorsal ACC. In addition, both the OFC and DLPFC activity correlated with self-report of decreased pain. These findings add a temporal component and suggest that the OFC can inhibit pain sensation by increasing activity in the anticipation of a painful stimulus.

Interestingly, this same pattern of brain activity was also observed during social pain. Subjects played a computer "CyberBall" game in which they believed they were playing with two other people on computers outside of the scanner (Eisenberger *et al.* 2003). Over time, the subject was excluded from the game and watched while the two (supposed) outside participants played with each other. The dorsal ACC was active during the exclusion period, and activity in this region was positively correlated with the amount of distress that the subject felt, suggesting that this dorsal ACC region also registers social pain. In addition, right VLPFC activity was negatively correlated with dorsal ACC activity, suggesting that the VLPFC was regulating neural activity related to the social distress of being excluded. These findings converge with the idea that right VLPFC mediates cognitive evaluation that mitigates neural activity associated with the affective component of pain.

However, it is not clear that a conscious evaluation of pain expectancy, or a reappraisal of the pain situation is necessary for the recruitment of lateral OFC/VLPFC activity to dampen pain related activity, since engaging in an unrelated cognitive task, such as a spatial maze, shows the same interaction of increased lateral OFC activity and decreased pain related activity in the somatosensory cortex as well as diminished discomfort (Petrovic *et al.* 2000). In addition, electrical stimulation of the lateral OFC leads to a decrease in pain-related behaviors in rats (Zhang *et al.* 1997), suggesting that the lateral OFC can suppress pain-related activity through neural projections, and conscious evaluation is not necessary.

12.6. **Regulation of affective information in selective attention**

In order to successfully achieve stated goals, it is crucial to selectively attend to information relevant to goal, and inhibit information that is irrelevant. Evidence suggests that the lateral OFC facilitates selective attention by controlling the interference of irrelevant emotional information in the environment on spatial attention. For example, Hartikainen *et al.* (2001) showed that OFC lesion patients could not regulate the influence of emotional primes on target detection. During the task, participants had to identify whether a briefly presented triangle in the right or left visual field was upright or inverted. Just prior to this target triangle, a positive, negative or neutral picture (from the IAPS collection) was centrally presented. Subjects were told to ignore the picture and do their best on the task. Due to an inability to inhibit the influence of the emotional primes, OFC patients' reaction times were particularly sensitive to the emotional priming conditions (Hartikainen and Knight 2001, Hartikainen *et al.* 2001). Healthy participants' reaction times were speeded up in positive emotion priming conditions and slowed down in negative emotion priming conditions (Hartikainen *et al.* 2000a). This effect of emotion prime on reaction time was significantly enhanced for patients with OFC damage (Hartikainen *et al.* 2001). The patients showed quicker reaction times to detect the target immediately after a positive picture and slower reaction times to detect the target immediately after a negative picture.

In addition, OFC lesion patients showed a different pattern of electrophysiological response, especially during negative emotion trials. Patients had enhanced neural activity in posterior regions (i.e. P200 amplitude) for the negative emotional stimuli, and, an abnormal pattern of slow wave neural activity during target detection, including increased slow wave positivity at posterior scalp sites, and reduced slow wave negativity at frontal sites. Together these data suggest that the OFC is involved in inhibitory modulation of posterior cortical brain regions when emotion influences attention. Without this top-down modulation, neural regions that process emotional information are neurally disinhibited, and, as a result, the emotional information has an exaggerated effect on attention.

This role for the lateral OFC in facilitating selective attention by inhibiting interference is also demonstrated in fMRI research. Vuilleumier *et al.* (2001) showed a display of two faces and two houses arranged horizontally and vertically around a fixation cross. Subjects were given instructions either to attend to the houses and ignore the faces, or attend to the faces and ignore the houses, and then identify whether the two attended stimuli were matching or not. The faces had either a neutral or fearful expression. The results showed that the lateral OFC was engaged when fearful faces had to be ignored in order to make a judgement about the houses. However, the lateral OFC was not active when ignoring neutral faces. In addition, posterior visual association cortex showed modulation based on spatial attention: activity in the fusiform gyrus face processing area increased when subjects attended to faces and decreased when faces were ignored. The findings suggest that the lateral OFC is involved in inhibiting the irrelevant emotional information to assist the subject in completing the task, and it further indicates that lateral OFC activity may facilitate enhanced attention by suppressing the neural activity associated with the representation of the interfering stimulus (Vuilleumier *et al.* 2001).

Bishop *et al.* (2004) looked at the influence of state anxiety on this task with the idea that people high in anxiety will have a harder time ignoring irrelevant threatening stimuli in the environment. They found that the left lateral OFC/VLPFC as well as left DLPFC were both involved in ignoring the fearful face. Specifically, they found an inverse relationship between statewise anxiety and VLPFC/DLPFC activity during blocks of trials that necessitated ignoring the fearful face. Healthy, non-anxious people show increasing activity in these regions in anticipation of a "to be ignored" fearful stimulus, suggesting that these subjects are employing VLPFC activity to help them suppress the interfering influence of the threat related stimulus when the emotional information is not relevant to the task. However, people high in anxiety did not recruit these regions to help them ignore the fearful stimuli, suggesting a failure in top down regulatory control in anxiety (Bishop *et al.* 2004).

12.7. **Emotion regulation**

The relationship between OFC mediated top-down inhibitory control and bottom-up representational activity in posterior and subcortical areas has been illustrated several times in studies of emotion regulation.

Emotion regulation refers to a variety of behavioral processes that individuals use to influence which emotions they have, when they have them, and how they experience and express them. It includes decreasing, maintaining or increasing both negative and positive emotions through rationalization, reappraisal, and suppression (Gross 2002). Investigations of the neural basis of emotion regulation suggest that multiple PFC regions, including the lateral OFC/VLPFC, control emotional experience and expression.

The neural basis of emotion regulation through suppression has been explored with feelings of anger, sadness, sexual arousal, and general negativity (Levesque *et al.* 2003, Beauregard *et al.* 2001, Blair 2001). For example, the OFC (BA 11) and VLPFC (BA 47) are active when subjects try to decrease their erotic feelings to erotic films as well as when they decrease their feelings of sadness to sad films (Levesque *et al.* 2003, Beauregard *et al.* 2001). Additionally, greater activity in the right OFC and right DLPFC was associated with more intense feelings of sadness during the suppression condition, indicating that more intense feelings of sadness required more OFC mediated inhibitory strength to suppress.

Reappraisal is a cognitive evaluation in which a person consciously re-interprets the meaning of a situation in order to change their emotional response to it. For example, the experience of getting fired from a job is usually distressing. A person's appraisal of the situation can increase or decrease negative affect associated with such an event. Engaging in a reappraisal strategy to decrease negative emotions associated with the event would include evaluations highlighting positive outcomes and emotions: "This is a blessing in disguise; the job was not right for me anyway. Now I am free to find a job that is better suited to me, and I can be happier." Reappraising the situation in such a way that increases distress would focus on negative outcomes and emotions: "Getting fired is the worst thing that could happen. I am worthless. I may never work again. I will not be able to support myself." Reappraisal as a means of decreasing distress is a relatively effective, healthy strategy for coping with emotionally difficult or aversive events (Gross 2002).

Decreasing distress by reappraisal employs VLPFC- and lateral OFC-mediated top-down regulation strategies which have their effect by decreasing neural activity associated with the representation of emotional feeling (Ochsner *et al.* 2002, Ochsner *et al.* 2004, Phan *et al.* 2005). For example, subjects were shown negative or neutral scenes and instructed to either allow themselves to feel whatever emotions came up for them or to reappraise the situation depicted in the scene in order to decrease their emotional response (Ochsner *et al.* 2002, Phan *et al.* 2005). When people allowed themselves to feel the full negative impact of negative scenes, regions associated with emotional feeling, such as the medial OFC, insula, and amygdala, were active; however, when subjects reappraised negative scenes so that their interpretation decreased their negative feelings, the VLPFC (inferior frontal gyrus BA 44, 10, 46) and the DLPFC were active (Ochsner *et al.* 2002, Phan *et al.* 2005). In addition, lateral OFC (Phan *et al.* 2005) and VLPFC (BA 44, 46) (Ochsner *et al.* 2002) activity during reappraisal was inversely correlated with activation in the amygdala. This is specific neural evidence that activity in the VLPFC has inhibitory effects on the neural representation of those feelings in the amygdala. Furthermore, an increase in bilateral VLPFC and bilateral DLPFC activity was related to a decrease in self-reported negative affect (Phan *et al.* 2005), illustrating that this neural dynamic ultimately has its effect on emotional experience.

Though both VLPFC and DLPFC activity have been observed in emotion regulation, there is evidence that lateral OFC is particularly involved in strategies employed to decrease negative affect. In a direct comparison of using reappraisal to increase negative affect (i.e. up-regulation) as compared to decrease negative affect (i.e. down-regulation), Ochsner *et al.* (2004) found that the lateral OFC was more active when using reappraisal to decrease as opposed to increase negative affect, and the DLPFC was more active when using reappraisal to increase as opposed to decrease negative affect. Consistent with the idea that amygdala activity is related to emotional experience, the amygdala was more active when subjects used reappraisal to increase their distress during picture viewing and less active when using reappraisal to decrease their distress. This modulation of amygdala activity occurred within 2 seconds of employing the reappraisal strategy (Ochsner *et al.* 2004). In addition, Phan *et al.*(2005) found that as activity level in the DLPFC and amygdala increased, so did the experience of negative affect. Together these studies suggest that the DLPFC is involved in broad regulatory control of experience, especially in bringing emotional representations on line, maintaining them, and strengthening them, whereas the lateral OFC is involved in the inhibition of these cortically represented feelings and images.

12.8. **Controlling the influence of mood congruent bias**

In the absence of regulation, feelings and moods can influence and distort perception, attention and judgement. Specifically, people have a bias towards attending to factors in their environment that are congruent with their mood, a phenomenon known as mood-congruent bias (Bradley and Mogg 1994, Bradley *et al.* 1995). For example, anxious people are quicker to detect threatening stimuli in the environment than non-anxious people; spider phobics are quicker to detect photographs of spiders among snakes and snake phobics are quicker to detect snakes among spiders (Ohman *et al.* The face in the crowd revisited: a threat advantage with schematic stimuli 2001, Ohman *et al.* Emotion drives attention: detecting the snake in the grass 2001). Depressed people are more likely than non-depressed people to interpret a neutral situation as negative (Gotlib and McCabe 1992, Gotlib and McCann 1984, Gotlib and Olson 1983). This has also been shown in the context of social interactions; after an experimental mood manipulation, subjects in a sad mood are more likely to judge a neutral face as sad and subjects in a happy mood are more likely to judge a neutral face as happy (Halberstadt and Niedenthal 2001, Innes-Ker and Niedenthal 2002). Without inhibiting this distorting influence, mood congruent bias can distort perception and perpetuate emotional disorders such as depression, and anxiety.

Researchers are starting to investigate the neural influences of mood congruent bias. For example, in a go/no-go task, depressed, non-depressed and healthy subjects were presented with sad, happy and neutral words (Elliott *et al.* 2002). In certain blocks of trials subjects responded by button press to happy words and withheld response to sad words or they responded to sad words and withheld response to happy words. Prior research indicates that depressed individuals are more attentive to mood-congruent sad words, and therefore have more difficulty ignoring these words when they have to be ignored. This additional effort needed to overcome mood-congruent bias is reflected in neural response; depressed individuals had more right lateral OFC/VLPFC activity when ignoring sad words (and attending to happy words) as compared to ignoring happy (and attending to sad words).

Mood-congruent bias has also been shown in risk-taking behavior; failure to regulate the influence of mood can lead to bad choices. Behaviorally, when people are in a good mood, they are more likely to underestimate the risk in a situation and engage in risky behavior, and, conversely, when people are angry or upset, they are more likely to overestimate risk and avoid risky behavior (Lerner and Keltner 2001). Therefore the mood you are feeling at a particular point in time will influence your judgement and behavior and this influence needs to be controlled in order to make good decisions. Beer *et al.* (in press) investigated the influence of mood priming on risk taking behavior in a hypothetical roulette/gambling task. Behavioral results showed that positive priming before making a bet led to a riskier choice, whereas negative priming led to a more conservative choice. Importantly, they found an inverse correlation with the left lateral OFC and the influence of mood priming on betting. The more activity there was in the left lateral OFC, the less influence mood had on their choice of bet. This shows that the lateral OFC regulated the influence of emotion on decision-making (Beer in press). Interestingly, the left lateral OFC was also involved when subjects were instructed to use the emotional information as part of their betting strategy. This suggests that the lateral OFC may be involved in inhibiting emotional information when it is irrelevant and integrating it when it is relevant to the decision. Additional research is needed to illustrate the relative role of the lateral OFC in inhibiting as compared to integrating emotional information during decision-making.

12.9. **Inhibitory control in attitude regulation and memory**

Lateral OFC- and VLPFC-mediated inhibition also regulates the influence of *a priori* belief and initial emotional response on reasoning and judgement. Goel and Dolan (2003) investigated the influence of *a priori* belief bias on logical reasoning. Deductive reasoning is the process of drawing valid conclusions from a given set of premises. Although it should be a “closed system”, drawing only from the given facts and information (thus safe from the influence of *priori* beliefs, feelings, and intuitions), one’s belief about the world can influence validity judgements about presented arguments. People are more likely to believe a logical argument when it fits with their *a priori* beliefs than the same type of argument when it conflicts with their beliefs. Consequently, if the logical conclusion is consistent with beliefs about the world, the beliefs are facilitatory with the logical task (and people do better), whereas a similarly logical argument in which the logical conclusion is inconsistent with the person’s belief, they are more likely to disagree with the logical argument (and falsely reject it as valid). Thus, rational and appropriate reasoning about a given set of facts or information often requires inhibiting a personal belief system to make a valid judgement. Without inhibiting one's personal belief, he is susceptible to belief bias in reasoning resulting in mistakes in logic and decision-making (Morley *et al.* 2004, Evans *et al.* 2001, Newstead *et al.* 1992, Evans *et al.* 1983).

Goel and Dolan (2003) had people identify the validity of a set of logical arguments. Some of the arguments were congruent with common beliefs about the world and some were equally valid arguments but contradictory to common world beliefs. Using fMRI they found that right OFC/VLPFC (BA 47, 45) was more active for correctly inhibiting belief bias as compared to error trials in which the belief bias led to faulty reasoning and the wrong conclusion. The VMPFC showed the opposite pattern. It was less active during the correct inhibition of belief bias but more active when the *a priori* beliefs led to incorrect reasoning (Goel and Dolan 2003). These findings illustrate that right OFC/VLPFC activity was related to resistance to belief bias and suggests that this region may have facilitated this resistance by inhibiting the influence of the *a priori* belief.

Initial emotional reactions to “hot” political or social topics can also cloud logical reasoning, and, in many cases, these initial reactions need to be suppressed. Cunningham *et al.* (2004) investigated the neural circuits of making explicit (good vs. bad) and implicit (abstract vs. concrete) judgements of socially relevant topics such as abortion, gun control, and sex education. They found that activity in the right lateral OFC was significantly correlated with the amount that people felt that they had to control or suppress their initial response to the concept. Interestingly, post-scanning questionnaires revealed that topics which required the suppression of automatic responses were often those topics that had both positive and negative qualities. Therefore these topics required more evaluation before a judgement could be made (Cunningham *et al.* 2003, 2004), suggesting that, perhaps, the process of evaluation suppresses the influence of emotional response on judgement.

These studies are consistent with memory research showing that left VLPFC activity facilitates working memory by inhibiting proactive interference (D'Esposito *et al.* 1999). Proactive interference occurs when a recent but irrelevant memory interferes with current recognition or recall. Looking for a parked car in an often used parking lot is a common situation that can create proactive interference, since the memory of parking in the past can interfere with the recall of the car's current location (Badre and Wagner 2005). Experimenters manipulate susceptibility to proactive interference in item recognition tasks by ‘luring’ subjects with items that were recently presented in the task, but are not the target on that specific trial. Greater left VLPFC activity is associated with a correct response on trials containing a familiar (“lure”) item. In other words, greater VLPFC activity is associated with resistance to proactive interference (D'Esposito *et al.* 1999, Badre and Wagner 2005). In addition, damage to the left VLPFC is associated with enhanced susceptibility to proactive interference (Thompson-Schill *et al.* 2002).

Together, these studies indicate that the inhibitory influence of the lateral OFC/VLPFC is not necessarily restricted to affective information, as is proposed by the Dynamic Filtering Theory, nor is it confined to negative (as opposed to positive) affect, as is proposed by the Distraction Theory. However, these studies do show that the lateral OFC and VLPFC help maintain goal oriented focus by suppressing the influence of interfering information. Furthermore, data on both belief bias and evaluative judgements are consistent with the idea that the VLPFC mediates a conscious, evaluative process, as is proposed by the Distraction Theory, which may suppress the influence of irrelevant information.

12.10. **Self-regulation in social contexts**

Appropriate and successful social behavior requires on line monitoring of the impact and appropriateness of one's comments and actions. Individuals must manage the conflict between inner impulses and external moral codes (Carver and Scheier 1990). Cues from the environment (e.g. the formality of a black-tie dinner) or social cues from another person (e.g. an angry response to a comment) provide information that is important to use to regulate one's own social behavior in that context. If, in the course of a social interaction, excessively friendly comments cause embarrassment or excessively aggressive comments cause anger, then one must inhibit those behaviors and develop a different way of communicating in order to build social relationships.

Numerous clinical anecdotes chronicle impulsive, selfish, disinhibited, socially inappropriate behavior of patients with lesions to the OFC. In one of the few empirical studies on inappropriate behavior in this patient group, Beer *et al.* (2003) investigated the regulation of social behavior in OFC lesion patients. The focus of these studies was to investigate whether self-conscious emotions, such as embarrassment, shame, guilt and pride, would help regulate social behavior in OFC patients as it does in healthy, normally functioning individuals. The results show that OFC patients are able to generate and feel self-conscious emotions but they do not use these emotions appropriately to regulate behavior (Beer *et al.* 2003).

In a self-disclosure task, subjects were presented with a set of emotional terms and asked to define each one, and give an example of when they felt that way. OFC patients inappropriately disclosed more intimate details than was necessary for the completion of the task. Similarly, in a teasing task, subjects were told to make up a nickname for two experimenters based on their initials. OFC patients exhibited inappropriately intimate and hostile teasing behavior such as sustained eye contact, intrusive body posture, playful gestures and prosody. In addition, they less frequently exhibited appropriate apologetic teasing behavior such as verbal apologies, submissive body posture, and blushing. Overall, they tended to tease strangers in an overly familiar way more suited to an intimate friendship or romantic relationship. In addition, they showed more pride in their teasing behavior, even though their behavior was inappropriate. These controlled experiments illustrate that the OFC patients are more likely to act inappropriately, and do not regulate their behavior based on on-line cues from the social situation.

Anger is another emotion that regulates behavior in social situations. When someone looks at you with an angry expression, it communicates disapproval and suggests that you should modify your current behavior. This has led to a suggestion that we have a social response reversal (SRR) system that is modulated by the disapproving negative cues of others (Blair and Cipolotti 2000). Lateral OFC may be involved in social reversals in both identifying that the behavior is wrong and in inhibiting that behavior and reversing course (Blair 2003, Blair 2004). For example, OFC lesion patients have difficulty identifying social reversal cues such as anger and embarrassment (Beer *et al.* 2003, Blair 2003, Blair and Cipolotti 2000), and in identifying actions that would make other people angry, such as identifying a social *faux pas* (Stone *et al.* 1998) or feelings of anger and embarrassment in story protagonists (Blair and Cipolotti 2000). In addition, neruroimaging studies show more right lateral OFC activity in response to angry expressions as compared to other facial expressions (Blair 2003, Blair *et al.* 1999). These data suggest that in addition to providing the neural mechanism of inhibition, the lateral OFC may also register and implement signals indicating the need to inhibit, such as an angry or embarrassed facial expression.

Furthermore, an inability to regulate an angry emotional response to others can manifest in aggressive tendencies, and these aggressive tendencies in high-risk individuals may be controlled by lateral OFC/ VLPFC function (Blair 2001, Blair 2004). Aggression research divides aggression into two types: reactive aggression in which a frustrating or threatening event triggers an impulsive aggressive act and instrumental (or proactive) aggression which is purposeful and goal directed (Barratt *et al.* 1999). Damage to OFC and medial PFC is associated with increased risk for the display of reactive aggression especially when the lesion occurs in childhood (Anderson *et al.* 1999, Eslinger *et al.* 2004, Grafman *et al.* 1996), whereas this damage is not associated with instrumental aggression. In addition, patients with a history of reactive aggression have reduced resting metabolism in lateral OFC (BA 47) (Raine *et al.* 1998a, 1988b, Goyer *et al.* 1994), suggesting that lower levels of neural activity in this region are associated with problems controlling aggressive tendencies.

12.11. **Conclusions**

The lateral OFC extending to the VLPFC shows regional and functional specificity in controlling information-processing and behavioral expression through inhibition. In particular, this neural region modulates the influence of emotional information on sensation, attention, judgement, emotional experience and expression by suppressing neural activity associated with the interfering or unwanted stimulus. The research reviewed here is consistent with well-documented evidence showing that the lateral OFC/VLPFC is the primary neural system governing the inhibition of habitual motor responses (Aron *et al.* 2003, Aron *et al.* 2004, Braver *et al.* 2001, Casey *et al.* 1997, Casey *et al.* 2001), and reversing or extinguishing reinforcement related associations (Iversen and Mishkin 1970, Roberts and Wallis 2000, Rolls 2000). Current research reveals that the lateral OFC regulates behavior by inhibiting the influence of a broad scope of sensations, feelings, thoughts, and actions.

12.12. **Future directions**

There are several issues regarding the inhibitory mechanism that need to be resolved in future research. First, it is not clear if there is a distinction between the inhibitory function of the lateral OFC (BA 11, 12, 47) and the VLPFC, particularly the more superior portions of BA 44, 45, in the frontal operculum. Many neuroimaging studies show inhibitory activity that extends across both regions (Levesque *et al.* 2003). Other studies of inhibitory control reveal two separate peaks of activity in the OFC and VLPFC (e.g. Phan *et al.* 2005), and, in other cases, different versions of the same inhibitory task will show peak activity in the lateral OFC in one study (Ochsner *et al.* 2004) and VLPFC in another (Ochsner *et al.* 2002).

Also, it is not clear if there are distinct functions of the right versus left lateral OFC/VLPFC during inhibition. Many inhibitory tasks show bilateral activations during inhibition (Wager *et al.* 2004). Other tasks show right but not left activity (Blair *et al.* 1999, Eisenberger *et al.* 2003, Goel and Dolan 2003, Levesque *et al.* 2003, Lieberman *et al.* 2004), whereas similar tasks show left but not right (Beer *et al.* in press, Bishop *et al.* 2004), and, different versions of the same task can produce relatively more activation in the right hemisphere in one study (Ochsner *et al.* 2004) and left in another (Ochsner *et al.* 2002). Though it is tempting to claim that more emotional tasks, such as emotion regulation, may employ right hemisphere systems (Levesque *et al.* 2003), and more cognitive tasks, such as the inhibition of proactive interference, use left hemisphere systems, this does not seem to be the case, since some cognitive tasks, such as modulation of belief reasoning, show only right hemisphere involvement (Goel and Dolan 2003), and some emotional tasks, such as inhibiting a fearful face, show only left hemisphere involvement (Bishop *et al.* 2004).

Understanding the distinction between the OFC and the VLPFC, as well as understanding the laterality effects during inhibitory tasks, will be enhanced by neuropsychological studies of frontal lobe lesion patients. Historically, most studies do not have enough well-defined patients to compare right and left lesion groups. However, a recent study with lesion patients reveals that the right VLPFC (BA 44, 45) is the region most associated with the ability to inhibit a motor response (Aron *et al.* 2003, 2004). Additional work needs to be done in order to see whether the right VLPFC is also the most primary region for the inhibition of emotion across a wide array of tasks.

Most of the research reviewed here investigates the regulation of negative information or negative affect. Few studies have investigated the neural substrates of inhibiting positive information or positive affect. Future work should help illuminate any differences in the neural substrates of regulating the effects of positive and negative affect on behavior.

Finally, evidence is clear that the lateral OFC/VLPFC governs inhibitory control. However, several studies suggest that it may play a dual role in both the inhibition and integration of emotional information on behavior (e.g. Beer *et al.* in press). Future work may reveal whether the lateral OFC/VLPFC is necessary for integration in addition to inhibition, and if so, what exact neural mechanisms or neuronal sub-populations facilitate the management of both of these processes.

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