Chapter 4
Context-Dependent Adjustments in Executive Control of Goal-Directed Behaviour: Contribution of Frontal Brain Areas to Conflict-Induced Behavioural Adjustments in Primates

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4.1 Introduction

Humans and animals frequently face the dilemma of selecting one out of several potential options to achieve their behavioural goal. Sometimes the choice is straightforward because all the available information about the benefit and cost of each option clearly indicate the suitability and priority of one of them for attaining the goal. However, in many occasions, the most appropriate option might not be immediately clear and therefore making a choice would require resolving the competition between the potential options. The concept of 'conflict' emerges when a decision should be made between such competing options. The conflict might emerge at sensory level between two or more sources of information or between competing actions (responses) or even between two or more behavioural strategies. In a changing/volatile environment the relative value (in terms of outcomes) of behavioural rules that guide actions in achieving goals might change and therefore selection of the most appropriate rule/behaviour would depend on updated estimates of the integrated cost and benefit of each option. In a changing environment, assigning value to each option would require consideration of alterations in factors such as the internal state of the subject (e.g. hunger, taste and the urge to achieve the goal), contextual information such as the associated cost and benefit of actions associated with each option and the recent outcome histories of decisions for the various available options. Imagine a person used to driving a car on the left side of streets in Japan

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moves to Korea and now faces the challenge of driving on the right side. In Japan, driving on the left side was the most appropriate option in fulfilling the contextual requirements and achieving the goal of safe driving. Such routinely performed and beneficial behaviour would become more habitual and act as a potentially valuable option in guiding behaviour. However, in a new environment the previous rule would no longer be beneficial and should be abandoned in favour of a new rule (right-side driving). Therefore competition/conflict would arise between the previous rule and the currently appropriate rule. Psychophysical studies have shown that such conflict between behavioural options adversely affects humans' behaviour in terms of accuracy and response time and appears as 'conflict cost' in various cognitive tasks. The behavioural effects of conflict are not limited to the current trial wherein the subjects experience the conflict between the behavioural options, but also extend to the following trials. Indeed, it is robust observation that after experiencing conflict, accuracy and response time are enhanced in the following trial when the subjects face the conflict again. Such an extended effect of conflict has been referred to as 'conflict adaptation' and is seen in many cognitive tasks. Theoretical models have emerged to explain the behavioural effects of conflict and the possible impact of conflict-induced behavioural modulation on adaptability of human behaviour in a changing condition. Influential models (Botvinick et al. 2004; Kerns et al. 2004; Carter and van Veen 2007) suggest that conflict in information processing is detected by brain areas such anterior cingulate cortex (ACC) and then conveyed to areas such as dorsolateral prefrontal cortex (DLPFC) to adjust the allocation of executive control to enhance resolving the conflict in the upcoming occasions. The conflict monitoring hypothesis explains the findings in various imaging studies (Kerns et al. 2004; Carter and van Veen 2007) that activation in ACC correlates with the magnitude of conflict experienced in the current trial and with the magnitude of behavioural adjustments and activation in DLPFC in the following trial; in addition, the activation in DLPFC in the following trials correlated with the magnitude of behavioural adaptation. Another alternative hypothesis proposed that ACC itself regulates the allocation of executive control based on the level of experienced conflict (Paus et al. 1998; Paus 2001; Posner and Rothbart 1998). An important implication of the conflict monitoring hypothesis is that it could effectively explain when and how allocation of cognitive resources was adjusted to enhance resolving the conflict between behavioural options and consequently support adaptive behaviour. The model was also expanded to explain error related changes in behaviour and the event-related potentials during conflict tasks. Imaging studies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are correlational and do not necessarily show whether a brain area is indispensable for a particular cognitive process or ability. However, additional studies also supported the conflict monitoring hypothesis by showing that activity of single cells in ACC, in patients undergoing surgical treatment, represent conflict in information processing (Davis et al. 2005) and that some patients with lesions involving ACC showed impaired conflict-induced behavioural adjustments (di Pellegrino et al. 2007).

However, findings from other studies in humans have not supported the proposed neural substrate of conflict detection and resolution processes. In separate studies, neuropsychological examination of patients with ACC lesions showed that the conflict-induced behavioural modulations were within the normal range (Vendrell et al. 1995; Stuss et al. 2001; Fellows and Farah 2005). These studies questioned the crucial role of ACC in mediating the conflict-induced behavioural adjustment. In addition, the results of some imaging studies indicated that while the participants performed more trials of conflict tasks, the behavioural effect of conflict was sustained while ACC activation gradually disappeared suggesting that ACC activation was not necessarily associated with the behavioural effects of conflict (Milham et al. 2003).

Studies in animal models provide the opportunity to implement various detailed neurobiological techniques such as single cell recording to examine the neuronal correlate of behaviour. In addition, lesion-behavioural studies in suitable animal models can reveal whether a particular brain area have an essential role in supporting particular cognitive ability. Whilst the conflict monitoring hypothesis gained support from numerous imaging studies in humans, some single cell recording studies in macaque monkeys could not find neuronal correlate of conflict in ACC (Ito et al. 2003; Nakamura et al. 2005). This discrepancy between findings in humans and monkeys led to intensive debate about the role of ACC in conflict monitoring. Currently, the neural substrate and the underlying mechanisms of conflict-induced behavioural and executive control adjustments still remain unclear. However, recent studies in humans and monkeys are starting to shed more light on the involvement of various brain areas and the underlying neural mechanisms in the conflict processing.

4.2 Conflict-Induced Behavioural Adjustment

4.2.1 Conflict Tasks Used in Psychophysical Studies in Humans

A well-studied paradigm used in humans to examine the behavioural effects of conflict is the Stroop test (MacLeod 1991; Botvinick et al. 2004; Kerns et al. 2004; Carter and van Veen 2007), in which participants are presented with the name of a colour printed in coloured ink and they must identify the colour of the ink as fast and as accurately as possible. In incongruent (high conflict) conditions, the colour's name differs from the ink colour, however in congruent (low-conflict) conditions the colour name matches the ink colour and in neutral condition, the word is not colour-related. A consistent observation is that the subjects are less accurate and slower in incongruent conditions (conflict cost). It is assumed that information regarding the ink colour and information regarding the word are processed separately, leading to distinct competing motor responses. The conflict cost has been

reported in other tasks such as flanker test, Simon test and Go-No-go tasks (Carter and van Veen 2007; Mansouri et al. 2009). Conflict can be also evoked between the emotional content and other attributes of stimuli and influence the behaviour (Braem et al. 2013; Etkin et al. 2011). The effects of conflict are not limited to the current trial and can also influence performance in the upcoming trial when the participants are required to resolve the conflict between competing choices again. To estimate the conflict-adaptation effect the difference in mean accuracy or response time is compared between high-conflict trials that are preceded by low-conflict trials (LH condition) and high-conflict trials that are preceded by high-conflict trials (HH condition). Conflict-adaptation effects appear as improved performance in resolving the conflict in HH trials (Kerns et al. 2004; Carter and van Veen 2007; Egner 2007; Mansouri et al. 2009). The conflict-adaptation effect has been observed in various conflict tasks such Stroop test. Flanker and Simon tests (Erickson et al. 2004; Mansouri et al. 2009).

4.2.2 Neural Substrate and Underlying Mechanisms of Conflict-Induced Behavioural Modulations

4.2.2.1 Imaging Studies in Humans

The conflict monitoring hypothesis (Botvinick et al. 2004; Carter and van Veen 2007) emerged from a series of imaging and event-related potential studies showing that in Stroop test and other conflict tasks, ACC was more active during high conflict trials; this led to the conclusion that the ACC was involved in the conflict-detection process (Botvinick et al. 2004; Carter and van Veen 2007). The hypothesis also proposed that other regions such as DLPFC which were more active in HH than in LH conditions were involved in mediating the executive-control adjustment required to deal effectively with sustained conflict (Botvinick et al. 2004; Kerns et al. 2004; Carter and van Veen 2007). Further studies (Fan et al. 2003; Kerns et al. 2004; Egner and Hirsch 2005a, b; Liston et al. 2006) provided support for this hypothesis by showing that in high-conflict trials the magnitude of ACC activity predicted the degree of behavioural adjustment and the activation level in the DLPFC on the subsequent trial. In addition, they showed that ACC activity in the second trial of the HH conditions was lower than that in the LH conditions and that the increase in DLPFC activity observed in HH trials tended to correlate with greater degrees of behavioural adjustment. These findings fit with the idea that conflict is detected by the ACC and signals adjustments in control, mediated by DLPF, that serve to effectively decrease the conflict in the 2nd trial of HH conditions. Although the conflict monitoring hypothesis has been focused mainly on the role of ACC and DLPFC in conflict detection and resolution, activation of other brain areas have also been shown in the conflict tasks.

Parietal Cortex Several imaging studies have shown activation changes in parietal cortex in conflict tasks (Casey et al. 2000; Barch et al. 2001; Adleman et al. 2002; Milham et al. 2003; Durston et al. 2003; Fan et al. 2003; Egner and Hirsch 2005b; Liston et al. 2006; Roelofs et al. 2006; Krebs et al. 2015). It has been suggested that parietal cortex might be involved in detection of conflict at the level of sensory processing (Liston et al. 2006). A recent imaging study (Krebs et al. 2015) showed that irrelevant incongruent information (words), which elicited conflict cost, led to improved subsequent memory for the relevant target stimuli (faces) and that the conflict induced memory benefit was selectively associated with activity modulations in the DLPFC and the parietal cortex suggesting that DLPFC and parietal cortex were involved in conflict-induced behavioural enhancement.

Insula Neuroanatomical and functional imaging studies suggest that the ACC and the insular cortex comprise a closely related functional network both during active task performance and at rest (Augustine 1996; Dosenbach et al. 2007; Nelson et al. 2010). Egner and Hirsch (2005a) reported that in the context of a face-word Stroop like test the behavioural performance was enhanced in HH trials and that fMRI signal in the right DLPFC and the left anterior insula were stronger in the HH condition than in the LH condition, suggesting that in addition to the DLPFC, insula may also be involved in conflict adaptation. Neuroimaging activation changes in insular cortex have also been reported in other versions of the Stroop test (Banich et al. 2001).

Cortical Areas around Inferior Frontal Sulcus Studies also suggest that areas around the junction of the inferior frontal sulcus and the inferior precentral sulcus also change activation in conflict tasks suggesting their involvement in cognitive control processes (Derrfuss et al. 2005; Sundermann and Pfleiderer 2012).

Cerebellum Alteration in cerebellar activation has also been observed in conflict tasks (Casey et al. 2000; Egner and Hirsch 2005b) and patients with cerebellar lesions exhibit higher conflict costs in the absence of task-switching costs (Schweizer et al. 2007). These findings suggest that the cerebellum may also play a crucial role in conflict processing, however the exact functional role of cerebellum remains unclear.

Orbitofrontal Cortex (OFC) The activation of orbitofrontal cortex during performance of the Stroop test has been seen in human imaging studies. Bench et al. (1993) conducted a PET study in humans performing Stroop test and observed activation in right OFC and cingulate cortex. Mitchell (2005) also reported activation of OFC during performance of Stroop test in a fMRI study. In addition, Goldstein et al. (2011) conducted a PET study in control and drug-addicted human subjects and showed that a higher activation in orbitofrontal gyrus was associated with higher conflict level. They suggested that OFC might be involved in the evaluation of conflict level to increase the mental efforts to improve the behaviour.

These studies in humans suggest that a distributed network of brain regions is involved in processing the conflict information and possibly mediating the behavioural effects of conflict. These imaging studies have greatly contributed to our understanding of the activation patterns in different brain regions but the findings are correlational and do not necessarily indicate whether these brain regions have any indispensable role in conflict detection or resolution. Further detailed neurobiological assessment are necessary to examine the essential function of these areas in conflict processing.

4.2.2.2 Studies in Non-Human Primates

Animal models provide the opportunity to conduct various detailed neurobiological investigations, however it was first crucial to show that conflict exerts similar behavioural modulations in such animal models. Conflict-related behavioural modulations have been reported in monkeys in the context of various tasks (Stoet and Snyder 2009). Lauwereyns et al. (2000) examined macaque monkeys' behaviour in an analog of Stroop test and showed conflict-related behavioural modulations. Ito et al. (2003) trained macaque monkeys to perform a saccade countermanding task in which the monkeys initiated a saccadic eye movement upon receiving a go signal. However, in a smaller proportion of trials a stop signal was presented and the monkeys had to stop their initiated or planned saccade. By varying the time between the go and stop signals the difficulty of saccade inhibition could be controlled. The animals' behaviour indicated a conflict cost that was presumably associated with competition between gaze-shifting and gaze-holding processes. The neuronal activity was recorded in ACC, however no modulation directly linked to the conflict level was found in the ACC cell activities. Nakamura et al. (2005) recorded ACC activity in the context of a conflict task requiring saccadic responses but did not find encoding of conflict in ACC cell activities. Mansouri et al. trained monkeys to perform a conflict task in which the conflict emerged between two behavioural rules (Fig. 4.1). Monkeys' behaviour showed a significant conflict cost as well as a robust conflict adaptation effect, however bilateral lesions within ACC neither affected conflict cost nor conflict adaptation. In contrast, conflict adaptation was significantly attenuated in DLPFC- and OFC-lesioned monkeys (Mansouri et al. 2007, 2014).

The absence of conflict encoding in ACC cell activity and intact conflict-induced behavioural modulations in ACC-lesioned monkeys were inconsistent with the predictions of conflict monitoring hypothesis. These apparently contradictory findings between studies in humans and monkeys led some investigators to conclude that conflict monitoring by ACC is a unique property of human brain function and non-human primates basically do not perceive and process conflict as humans do (Cole et al. 2009, 2010). They proposed that the reported conflict-related behavioural modulations in monkeys and other animals performing conflict tasks might be related to the other aspects of the task (Cole et al. 2009, 2010). A crucial question also emerged as to whether conflict is a separate entity that could be encoded in neuronal activity independent from other aspects of the task. Mansouri et al. (2007,

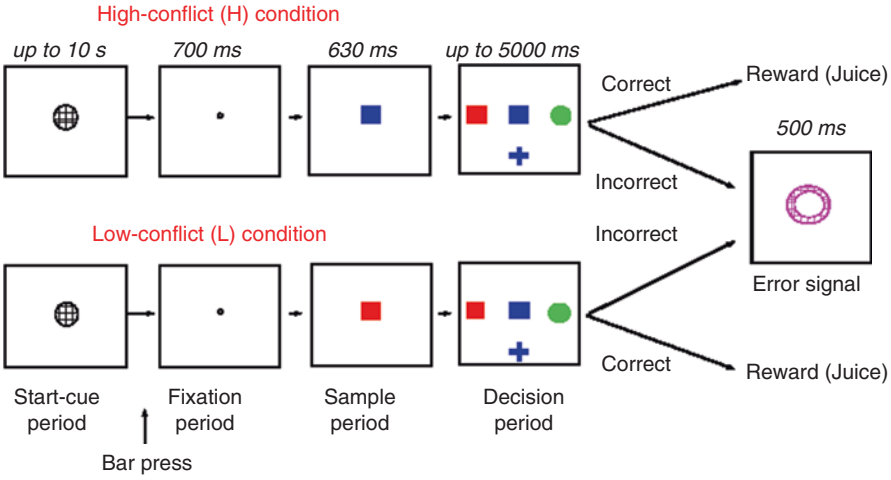

Fig. 4.1 In each trial, a start cue appeared when an inter-trial interval was over. The bar pressing changed the start cue to a fixation point. If the monkey kept pushing the bar and maintained its gaze on the fixation point for 700 ms, a sample stimulus replaced the fixation point. If the monkey maintained eye fixation and bar press for another 630 ms, three test items appeared (to the left, right and below the sample). The relevant rule for matching (matching by shape or matching by color) was consistent within a block of trials, and it changed without any notice to the monkey when a criterion of 85% correct performance was achieved. The relevant rule was not cued and the monkeys were only able to identify it by applying a rule and then interpreting the reward or error feedback in the context of the applied rule. Twelve and twenty four samples were shown in the low-conflict and high-conflict conditions, respectively

2009, 2014) recorded neuronal activity in DLPFC and OFC of monkeys performing a variant of Wisconsin Card Sorting Test (WCST) in which the competition between rules led to conflict cost and also conflict adaptation in monkeys' behaviour. These studies showed that activity of single neurons in DLPFC and also in OFC were significantly different between low-conflict and high-conflict conditions and that the conflict was encoded independently of the other aspects of the task such as the features of the visual stimuli or the behavioural rule or the upcoming actions. These findings suggested that both DLPFC and OFC cell activity encoded conflict as a separate variable (Fig. 4.2). The encoded conflict information was also maintained in the neuronal activity across the trials in DLPFC, but not OFC, cell activities (Fig. 4.3). This suggested that information of experienced conflict was retained by mnemonic processes in the neurocircuitry of DLPFC even after the conflicting situation was already over; hence such maintained information could be potentially used to evoke behavioural adjustment in the upcoming trials (Mansouri et al. 2007, 2009, 2014, 2015).

A few studies in humans have been able to record single ACC cell activity in patients undergoing surgeries. Davis et al. (2005) recorded ACC cell activity while the subjects performed versions of Stroop test (Counting and emotional interference) and found that neuronal activity was significantly different between low- and

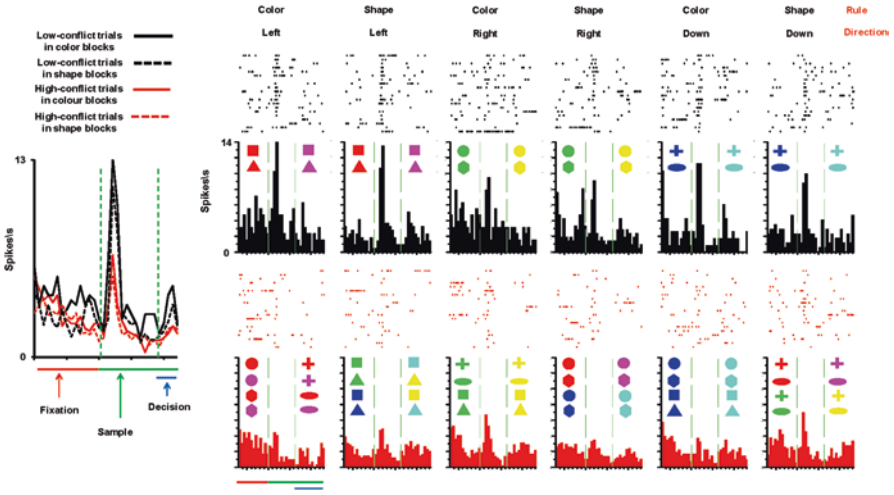

Fig. 4.2 Representation of conflict level in orbitofrontal cortex cell activity. The leftmost peri-stimulus time histograms (PSTH) show activities in low-conflict and high-conflict trials when colour- or shape-matching rules were relevant. Each column of the right histograms shows activities in low-conflict (upper) and high-conflict (lower) trials that required the application of the same rule and responses in the same direction. The raster-grams show spikes in individual trials. Samples presented in each condition are shown above individual histograms. Bin width is 50 ms for the leftmost PSTH, and 20 ms for other PSTH. Left and right vertical broken lines indicate the sample and test items onset, respectively. Only correct trials were included. The difference in activity between the low- and high-conflict conditions was seen independent of the rule, stimulus identity or the upcoming response direction

high-conflict conditions suggesting that conflict was encoded in ACC cell activities. In a recent comprehensive study, Sheth et al. (2012) conducted imaging, single-cell recording and lesion-behavioural studies in humans performing a conflict task. All the patients expressed behavioural effects of conflict that appeared as conflict cost and conflict adaptation and the fMRI showed a higher activation in ACC and in DLPFC in the high-conflict condition. The activated foci in ACC were then targeted for single-cell recording and subsequently for lesion study. Importantly, after selective lesions were made in the same regions within ACC, the behavioural effect of conflict in the current trial (conflict cost) remained intact but, the conflict adaptation effect was significantly impaired. This study provided solid evidence for encoding of conflict information in human ACC neurocircuitry. These finding appeared in contradiction to the findings in monkeys, however two recent studies have shown that in monkeys, ACC cells encode conflict independent of the other aspects of the cognitive task.

Ebitz and Platt (2015) trained monkeys to perform a conflict task in which conflict emerged between two different oculomotor responses or between task relevant and task irrelevant information. They found that both types of conflict influenced the monkeys' behaviour and the activity of ACC cells encoded the conflict level and errors. In addition, the ACC cell activity conveyed information about the current

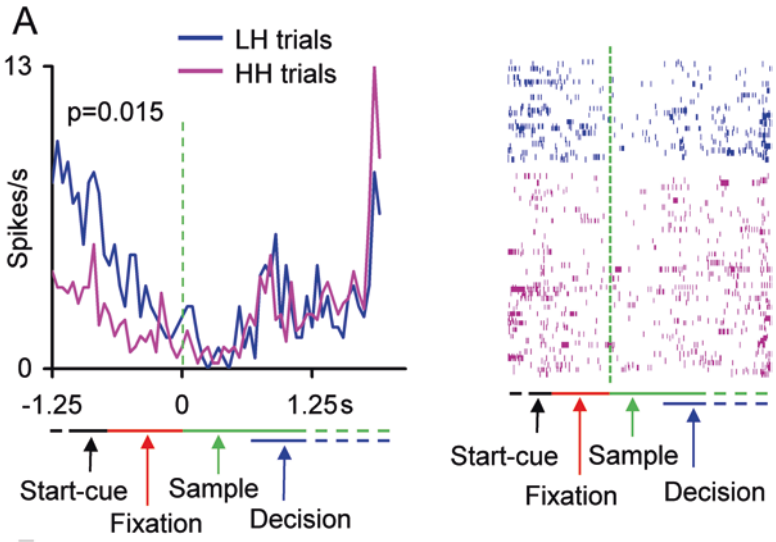

Fig. 4.3 Representation of history of conflict level in dorsolateral prefrontal cortex cell activity. Activities in high-conflict trials after low-conflict trials (LH, blue) and those in high-conflict trials after high-conflict trials (HH, pink) are shown for a single cell. The mean activities are aligned at sample onset. Only activities in correct trials that were preceded by correct trials were included. The p values show the significance level of activity difference in the fixation period between HH and LH trials. Bin size is 55 ms

pupil size or upcoming adjustments in the pupil size. This suggested that the ACC cell activity conveyed information about conflict-related adaptive changes in pupil size and presumably the arousal level. In another study, Michelet et al. (2016) trained monkeys to perform a conflict task in which the conflict arose between associated colour of a particular object with its presented colour. Behavioural effects of conflict was detected in the current (conflict cost) and in the following trial (conflict adaptation). Activities of a small but significant proportion of ACC cells conveyed information about the conflict level, however these conflict-related activity modulations were seen only in correct trials. Although conflict adaptation was seen in the monkeys' behaviour, information regarding conflict level in the previous trial was not represented in the ACC cell activity. These two studies, in the context of different conflict tasks, have clearly shown that ACC cells in monkeys convey information about the conflict independent of the other task-relevant events.

Conclusions made through neuropsychological examination of patients with ACC damage have necessarily been limited by the heterogeneity and inconsistency of lesions across patients. Furthermore, patients receive recordings/stimulation/lesions to ACC for clinical reasons indicative of significantly disturbed (from normal) brain function so inferring strong conclusions from such patients about normal brain function needs to be done with great caution. In this respect it is crucial and highly informative that we now have a few lesion-behavioural studies in animal

models wherein lesions that are more circumscribed and reproducible across animals, and which can be introduced into animals with normal pre-lesion brain function; these studies have to-date examined the role of a number of different cortical regions in conflict-cost and conflict-induced behavioural adaptation and their findings are.

Conflict Cost Mansouri et al. (2007, 2009, 2014, 2015) reported that bilateral lesions in DLPFC or ACC or OFC or superior part of dorsal lateral prefrontal cortex (sdlPFC) or posterior cingulate cortex (PCC) or frontal pole cortex do not impair the behavioural effects of conflict in the current trial (conflict cost). This indicates that other brain areas might mediate the conflict cost or it might result from mutual inhibitory effects between the neural processing related to competing options (responses). Different sensory-perceptual processes or the related actions might compete for controlling the behaviour and mutual inhibition between such parallel processing pathways might lead to slowing in reaching a final decision about one of the competing options.

Conflict Adaptation Mansouri et al. (2007, 2009, 2014, 2015) showed that bilateral lesions in ACC or PCC or sdlPFC or frontal pole cortex did not impair behavioural effects of conflict in the upcoming trials (conflict adaptation). However, bilateral lesions in DLPFC or OFC significantly attenuated the conflict adaptation indicating that DLPFC and OFC play an indispensable role in mediating the conflict-induced behavioural modulation and presumably in conflict-induced executive control adjustments.

4.3 Conclusion

Limitations in cognitive resources necessitate adaptive adjustment in allocation of these resources to optimize behaviour for achieving goals in changing environments. Conflict-induced behavioural adjustment has been extensively studied in the last two decades leading to influential hypothesis regarding context-dependent executive control adjustment. Studies in humans and non-human primates indicate great similarities in conflict-induced behavioural modulations. Recent studies in humans and monkeys have further advanced our knowledge regarding the neural substrate and underlying mechanisms of conflict processing and related behavioural alterations. Taken together these studies now indicate that a wider than previously appreciated distributed neural network might be involved in representation of conflict and mediating its effects, however within this network both DLPFC and OFC play indispensable roles. While ACC has long been considered a key component, the activations of ACC in conflict tasks might not be necessarily related to its role in conflict monitoring but may instead reflect ACC function in other cognitive domains such as adjusting the concomitant autonomic and affective aspects of the task and/or a role in action valuation and selection processes (Rushworth et al. 2004;

Kennerley et al. 2006, 2011; Euston et al. 2012; Shenhav et al. 2013; Heilbronner and Hayden 2016; Kolling et al. 2016).

Conflict is an abstract entity that might emerge in different contexts and between different elements of cognitive processes. DLPFC and OFC might be crucially involved in extracting and encoding conflict information in different contexts. In addition, mnemonic processes, mainly mediated through DLPFC, might support conflict-induced behavioural modulations by maintaining conflict information within and across trials. Studying conflict-induced behavioural modulations has opened a window to better understand the executive functions in primate brain and to gain insight to deficits in executive functions that is a hallmark of major neuropsychological disorders.

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