Master Thesis:

Can the negative deflections found with EEG on frontocentral electrodes be explained by one underlying process?

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Outline

Introduction

Electroencephalography (EEG) is an non-invasive method to measure brain activity in healthy subjects. By measuring the electric field on the subjects scalp, researchers are trying to identify different processes, brain states, brain oscillations or find markers of mental diseases. An event-related potential (ERP) is a segment of the EEG signal starting from a specific event, most of the time on stimulus or response onset. These ERPs can be averaged, to create a smooth waveform with positive and negative deflections. In the literature a lot of specific deflections are found to be generated by certain stimuli, be modulated by a certain condition or differ between groups of subjects. This thesis is looking at several negative deflections found on the frontal central electrode apparent generated by different processes, however they look similar. Can these be in fact be generated by the same underlying process?

In the first chapter I will introduce these negative deflections and argue why these could be produced by the same underlying process and/or the same area. In the second chapter I discuss the negative deflections in more depth. What kind of manipulations modulate the negative deflections? Are there similarities between the negative deflections? The third chapter is all about 3 important models that are able to explain a subset of the negative deflections and/or the function of the related area producing the negative deflections. Which of these models is correct? How can we differentiate the models by experimental data? In the last chapter I discuss studies that favor one model over the other and finally conclude whether the negative deflections are indeed produced by the same process and/or the same area.

Chapter 1

The frontocentral negativities. The same or different?

In this chapter we will introduce how the different negativities on the frontocentral electrode were found and argue why we could assume they are the same negativities produced by an underlying process.

The Negative Deflections

One of the most studied ERP-component may be the P300 and is supposed to be sensitive to task relevence and stimulus probability. The P300 was divided in an frontal component, P3a, and a component maximal over parietal cortex, P3b. Both with different functional functions: the P3a reflects orienting of attention and the P3b updating of working memory (Donchin et al., 1988). The N2, referring to the second negative peak in the average ERP waveform, was commonly found in combination with the P3a/P3b, and thereby called the "N2-P3 complex". Pritchard et al. (1991) made a influential classification scheme of the N2. The N2 was divided in three subcomponents, the N2a, N2b and the N2c. The N2a has a more modern name, the mismatch negative (MMN) in the auditory domain and the visual MMN in the visual domain (Czigler, 2007). In comparison with the N2b and N2c, the N2a does not require attention and is normally not accompanied with an P3. The N2b, or the No-go N2 (Ford et al., 1985), was larger for non-targets than to targets but elicited by both, has a (fronto)central scalp distribution (for visual and auditory stimuli) and is accompanied by a P3a. The N2c has a different scalp distribution for visual (posterior) and auditory (frontocentral) modality and the latency covaried with the reaction time.

In this thesis we are looking at negative deflections that are similar to the N2b, by having a frontocentral scalp distribution, not being modality specific and have an onset around 200 ms after stimulus onset (figure 1). Beside a negative deflection larger for non-targets, there is also a negative deflection found in the oddball task for unfrequent targets compared to frequent distractors (Nieuwenhuis et al., 2003) and tasks where there is conflicting information (Kopp et al., 1996), like the Erikson's flankers and Stroop task. A similar negative deflection is seen larger for rare/novel stimuli than for frequent/common stimuli and is called the novelty N2 (Courchesne et al., 1975). While all the above mentioned negative deflections (No-go N2, N200 and novelty N2) are elicited before a response, another set of negative deflections occur after a wrong response. The error related negativity (ERN) and the feedback-related negativity (FRN) also have a frontocentral scalp distribution. The

ERN is a response-locked negative deflection (50 ms after the response) that is larger for errors than correct responses (Falkenstein et al., 1991) and the FRN is a negative deflection around 250 ms after stimulus onset that is larger for negative feedback than positive feedback (Miltner et al., 1997). All these negative deflections all are found on the frontocentral electrode in ERP studies. Some relate to the stimulus, others to the response. Could they be generated by the same neural group or are they different processes? And how can we tell?

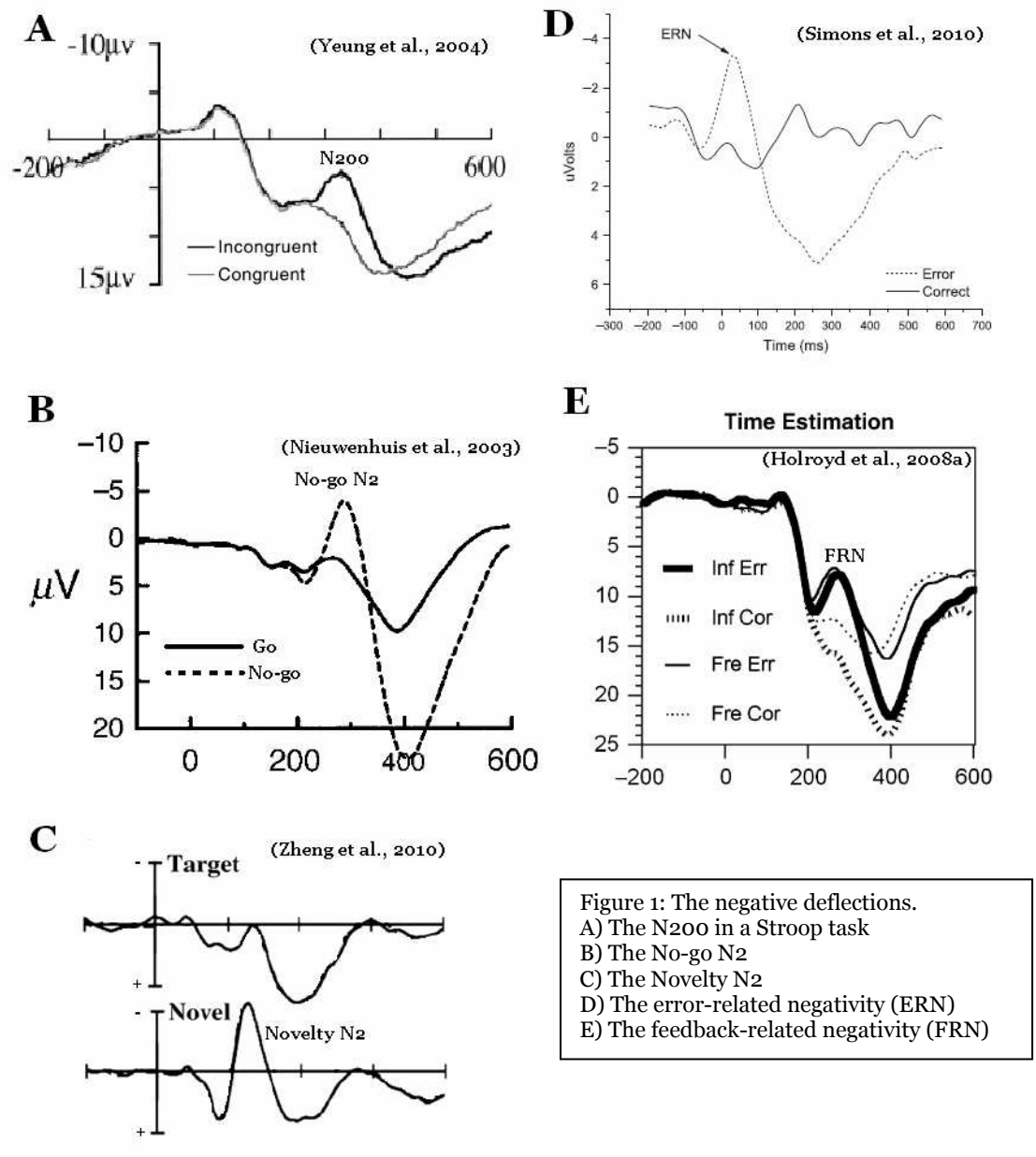


Figure 1: The negative deflections.
A) The N200 in a Stroop task
B) The No-go N2
C) The Novelty N2
D) The error-related negativity (ERN)
E) The feedback-related negativity (FRN)

Source Localization

The first avenue to answer these questions is by looking at the scalp distributions and dipole sources that are generated by these ERP components. Another way to compare sources of ERPs is by comparing the scalp distribution it produces. When two ERPs come from the same source the scalp distribution should also be the same, although the magnitudes might be different. When comparing the scalp distributions of the novelty N2 (Zheng et al., 2010), No-go N2 (Nieuwenhuis et al., 2003), the N200 (van Veen et al., 2002), the ERN (Dehaene et al., 1994) and the FRN (Miltner et al., 1997) they look very similar just on visual inspection (figure 2). All negative deflections are largest on the FCz electrode. Although the spatial resolution of EEG is not as good as fMRI, it has his statistics for source localization. By comparing the differences between electrodes an estimate of a source (dipole) can be made. The source dipole localizations of the No-go N2 (Nieuwenhuis et al., 2003), N200 (van Veen et al., 2002), ERN (Dehaene et al., 1994) and FRN (Miltner et al., 1997) all have a dipole in the vicinity of the anterior cingulate cortex (ACC). fMRI studies on the No-go N2 (Nakata et al., 2008), N200 (van Veen et al., 2002), the ERN (Carter et al., 1998) and the FRN (Holroyd et al., 2004a) validated the dipole locations found in the ERP studies. Both the dipole localizations and the fMRI studies pointed especially the dorsal anterior cingulate cortex (dACC) as the source for the No-go N2, N200, the ERN and the FRN. No fMRI studies or dipole analysis are done for the novelty N2. Most studies on novelty focuss on the P3a, mentioned above.

Comparative Studies

The visual inspection of the scalp distribution, source localization suggest that all the ERP components might indeed be the same process. And some fMRI experiments validated the dipoles at the locus of the process to be the ACC. However these comparisons are based on visual comparisons of scalp distributions and dipole sourse localization between studies. To statisticly test whether 2 negative deflections are the same, studies have to compared two negative deflections directly.

The first direct comparison we mention is between the N200 and the ERN (van Veen et al., 2002a). Using a flanker task they showed that the ERN and N200 have similar scalp distribution and dipole localizations. Holroyd et al. (2008) compared the N200 and the FRN. The scalp distributions and latencies of the N200 and the FRN, after an oddball stimulus or infrequent negative feedback stimulus respectively, were found to be not statistically different, suggesting that the N200 and the FRN are the same ERP component. A comparable analysis was done between the No-go N2 and the N200 (Nieuwenhuis et al., 2003). When the probabilities of the No-go and go stimuli were varied from a standard Go/No-go task (80% go; 20% no-go) to an standard oddball task (20% target; 80% non-

target), they saw a N2 enhancement to no-go stimuli in the Go/No-go task and to targets in the oddball task. Although the enhancement was larger in the 20% no-go condition than in the 80% no-go condition they concluded that both are the same, again because they have scalp distributions.

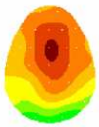
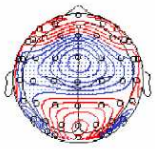
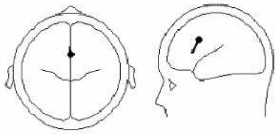
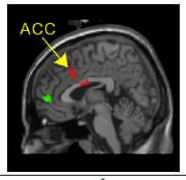
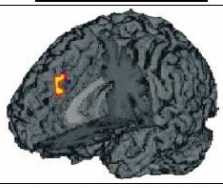
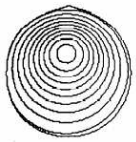
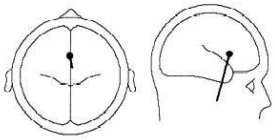
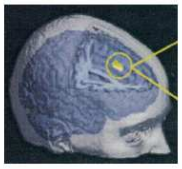
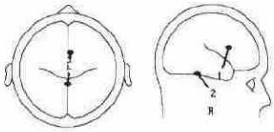
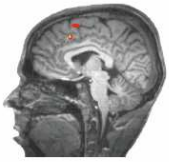
	Scalp distribution	Dipole source localization	fMRI
Novelty N2 (Zeng et al., 2002)			
No-Go N2 (Nieuwenhuis et al., 2003) (Nakata et al., 2008)			
N200 (van Veen et al., 2002)			
ERN (Dehaene et al., 1994) (Carter et al., 1998)			
FRN (Miltner et al., 1997) (Holroyd et al., 2004)			

Figure 2: Scalp distributions, dipole sources and fMRI activations found in ERP and fMRI study on the novelty N2, No-go N2, N200, error-related negativity (ERN) and feedback related negativity (FRN). On visual inspection all the scalp distributions look the same. Also the dipole sources are located in the anterior cingulate cortex for the No-Go N2, N200, ERN and FRN. This is validated by fMRI.

Summary:

In the literature several frontal-central negativities have been found. Most prominent are the No-go N2, N200, novelty N2, ERN and the FRN. Can these negative deflection be generated by the same process or are they indeed due to seperate processes? If they were the same process they all should be generated by the same neural structure. No statistical difference in scalp distribution were found between the negative deflections when compared, suggesting a similar dipole for all negative deflections. Also fMRI studies indicate that the dorsal anterior cingulate cortex is the generator of the No-go N2, N200, ERN and the FRN. As all negative deflections seem to be generated by the ACC, one underlying process might be responseible for all these negative deflections.

What could that process be? To find clues about this process I will discuss which experimental manipulations modulate these negative deflections in the next chapter. Beside experimental manipulitions it is also useful to look into the fMRI literature in what kind of tasks the anterior cingulate cortex (ACC) is more active.

Chapter 2
Negative deflections and Anterior Cingulate Cortex

In this chapter we will look closer at each negative deflection. What kind of manipulations have an effect on the amplitude or latency of the deflection? We start with a closer inspection at the stimulus-related negative deflections, the No-Go N2, the N200 and the novelty N2. Then we move on to the error-related negative deflections, the ERN and FRN. Although the negative deflections are the main focus of this chapter, we close the chapter with a closer look at the anterior cingulate cortex (ACC). According to the dipole source localization and fMRI studies this is generating the negative deflections.

No-go N2

In the Go/No-go task to some stimuli (targets) a response is needed, normally a button-press, while on other targets (non-targets) the subject has to withhold a response. The main result is the No-go N2 allready discribed above, the N2 of the non-targets is larger than the N2 of the targets (Ford et al., 1985). The No-go N2 is though to reflect a response inhibition process. Beside the standard task of only 2 stimuli, where one is a non-target and the other a target, several variations are possible. The subject can make a covert (e.g. silent counting) or overt (e.g. button press) response, multiple non-targets or targets (Azizian et al. 2006), the use of different modalities (Nieuwenhuis et al., 2004) and the probability that a target or non-target would occur can be manipulated (Nieuwenhuis et al., 2003). Several observations of the No-Go N2 have been made in the literature. First of all, the N2 is larger for overt responses than covert responses (Bruin et al., 2002). Second there is an increase in amplitude of the No-go N2 when the instructions emphasize speed over accuracy (Jodo et al., 1992).

The next set of studies look closer to No-go N2 in relationship with the expectancy for a target/non-target. A study, looking at an expectancy effect during a Go/No-go task, showed that activation of the anterior cingulate positively correlated with the lenght of the string of Go-trials (length of 1,3 or 5 go-trials) before a No-go trial (Durston et al., 2002). But using fixed strings of stimuli has some disadvantages. They assumed that subjects expected a No-go trial more after longer go-trials sequence. This is true on random sequences, but subjects probably figure out that the string of go-trials is manipulated, with a No-go trial always on even positions in the string and never a No-go trial after a No-go trial. Knowing the nature of

this manipulation and the fact that 20 No-go trials were given at each lenght, gives considerable doubt whether a No-go trial after the 3th Go-trial is more expected than after the 1st Go-trial. Therefor Smith et al., (2010) used a random sequence where the target and non-target are equiprobable. For each point they looked at the previous 3 stimuli and if there was and alternation (A) or a repetition (R) between first and second, ..., and the third and fourth. They found a modulation of the amplitude of No-go N2 when the target or non-target wasn't expected. A non-target after a repetition of 2/3 targets (and vice versa) or a sudden repetition after a period of alternation gave rise to a larger N2 amplitude. However assuming that subjects are expecting that a certain period (alternation/repetition) will progress during a random sequence is a point of discussion. A cleaner way to change the expectancy of the No-Go N2 is by changing the probability that non-target occurs compared to targets. Nieuwenhuis et al., (2003) manipulated the probability of non-targets and found that the No-go N2 is larger when non-targets are rare (20%) compared to a condition where target and non target are equiprobable.

Novelty N2

Courchesne et al. (1975) was the first that really showed a novelty N2. He used a frequent background non-target (80%) and a rare silently counted target (10%) and either rare simple trial-unique novels (10%), consisted of words, shapes and faces, or rare trial-unique complex novels (10%), consisted of a random colored patterns. The novels were also non-targets. Both the simple and complex novels were able to give a larger anterior N2 compared to the frequent non-target and the equally rare target, although the complex novels were more effective and gave a larger N2 than the simple novels. Another interesting point in his research was that the N2 of both novels didn't change when they became targets. But another question arises from this experiment. What makes a stimulus novel? In Courchesne the simple novels where as unique as the complex novels, but the complex novels gave rise to a larger anterior N2 nevertheless.

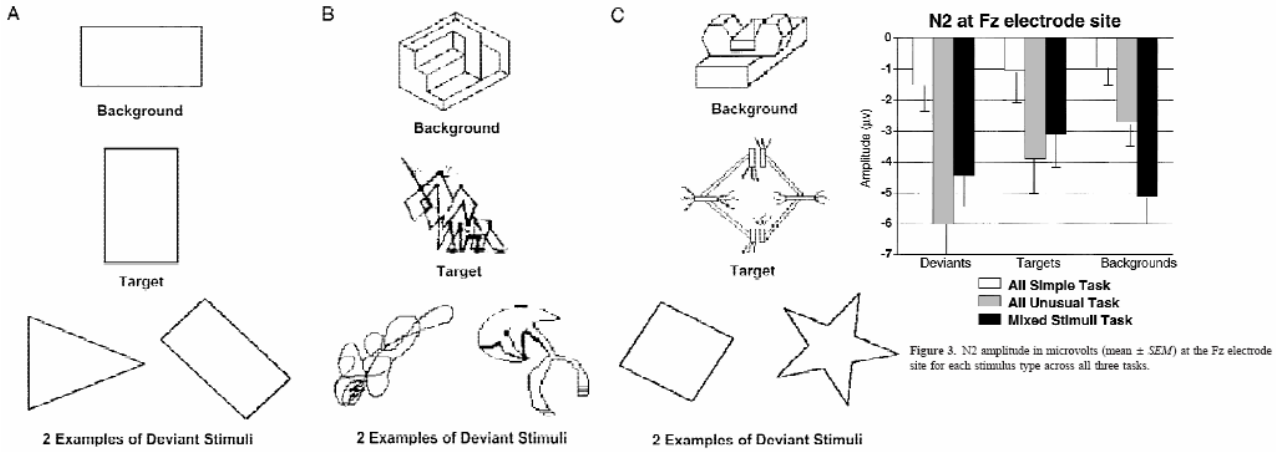


Figure 3. N2 amplitude in microvolts (mean ± *SEM*) at the Fz electrode site for each stimulus type across all three tasks.

Figure 1. Examples of the repetitive background stimulus (70% frequency), target stimulus (15% frequency), and deviant stimuli (15% frequency) from the (A) all simple task, (B) all unusual task, and (C) mixed stimuli task.

Figure 3: What is novel. In 3 sets of stimuli (A, B, C) Daffner et al., (2002) tested the effect of unfamiliarity/complexity and difference in category on the novelty N2. He saw a mixed result. The N2 of the deviants were larger in the all complex set (B) compared to the all simple set (A), suggesting modulation by complexity. But the simple deviant stimuli in the mixed set (C) had larger N2 than the simple deviant stimuli in the all simple set (A), suggesting a modulation because of the difference in catergory.

With a variety of stimuli (figure 3) Daffner et al. (2000) tested whether unfamiliarity/complexity of the stimulus is the reason for eliciting a novelty N2 or the difference in category between novel/deviant stimuli and the target and background. What he found was a mixed result. The comparison between the deviant stimuli in the mixed stimuli task and the stimuli in the all simple task showed an enhanced anterior N2 suggested that the difference in category drives the enhancement. On the other hand the comparison between complex stimuli and simple stimuli showed that the N2's of all the complex stimuli were larger than all the simple stimuli in the all simple condition. So the novelty N2 seems to be sensitive to both unfamiliarity (of long term experience) and deviation in category of the background and target stimuli.

N200

The N200 has been seen as a negative deflection around 200-300 ms after stimulus presentation. It is elicited when a target was unfrequent (Donkers et al., 2004), or by conflicting stimulus attributes (Mattler et al., 2006). The main task showing the N200 for unfrequent stimuli is the oddball paradigm. The oddball paradigm was first used in the 1980's (Towey et al., 1980). The standard oddball task is very similar to the go/no-go task. In a train of stimuli, the subject has to covertly (silent counting) or overtly (e.g. button press) response to the rare target stimuli and ignore the frequent background stimuli, while in the standard go/no-go the frequent targets need response (go-stimuli) and the rare nontargets don't (no-go stimuli). An enhanced anterior N2 has been seen to the rare targets compared to the frequent non-targets (Nieuwenhuis et al., 2003)(Holroyd et al., 2008). Nieuwenhuis et al.

(2003) showed that the oddball and Go/No-go N2 are the same and depend on unfrequency despite being a target or non-target.

A classical task to test conflicting stimulus attributes is the Erikson flankers task. In the Erikson flankers task the N200's amplitude seems to be larger in slow RT trials compared to fast RT trials and larger for incongruent trials compared to congruent trials. Its latency increased with RT and is also larger on incongruent compared to congruent trials (Yeung et al., 2004). During a stop-signal task (Logan et al., 1985) the N200 is larger for instructions that emphasizing speed over accuracy (Band et al., 2003), the amplitude is larger (Boxtel et al., 2001) and the latency (Kok et al., 2004) is longer in unsuccesful than succesfull trials. The amplitude is also larger when there is a long stop-signal delay compared to a short stop-signal delay (Ramautar et al., 2006). An enhanced N200 is only found when incongruent flankers coded for response incongruency (target and flankers coded for different response) but not for stimulus incongruency (target and flankers were different but coded for same response) (Van Veen et al., 2002a).

Matching tasks also elicit a frontal negative deflection. In the sternberg paradigm a larger N2 was elicited when the probe item was not in the memory set compared to a probe item that was presented in the memory set and the effect was strongest when the memory set only consisted of 1 item (Kotchoubey et al., 1996). In a sequential matching task, two paired stimuli either match or not, with 2 stimuli that could match in 2 different dimensions, color and shape, the anterior N2 showed a nice gradient: largest for complete mismatch, intermediate for a mismatch on one dimension and a small N2 for a complete match (Wang et al., 2004). This has also been shown for single dimensions, for color (Cui et al., 2000), shapes (Wang et al., 2003) and pictures (Wang et al., 1998). Even when the change was in a dimension not relevant for the test (Jia et al., 2007).

Error-related negativity (ERN)

The ERN was found at the same time by two different groups (Falkenstein et al., 1990)(Gehring et al., 1993) 80 ms after initiation of the wrong response/error measured with electromyography (EMG). The latency seems to be very consistent across experimental conditions (Falkenstein et al., 2000). The amplitude of the ERN increases when participants are motivated and when accuracy was prefered over speed (Gehring et al., 1993). In a study where errors could be made by using the wrong finger, the wrong hand or both, the ERN was largest when the response was made with the wrong finger and the wrong hand, suggesting that the ERN is sensitive to the degree of the error (Bernstein et al., 1995). It also seems that the process that produces the ERN is independent of what caused the error, whether the error was commited by the hands, feet (Holroyd et al., 1998) or eyes (Nieuwenhuis et al., 2001). When speed is emphasized, an ERN is also elicited when the response is slow, even

when the response is correct (Luu et al., 2000). The amplitude of the ERN also correlates with later error correction in the same trial. The larger the ERN, the higher the probability is that an error gets corrected (Gehring et al., 1993). When an error is corrected the ERN was larger on fast corrected trials than on slow corrected trials (Rodriquez-Fornells et al., 2002). Not only is the ERN elicited by a response error, but seeing someone else making a mistake also produces an ERN (Bates et al., 2005)(van Schie et al., 2004). The ERN is also generated when a task goal has not been achieved (Tokoyama et al., 2005). Finally, awareness is not necessary for the generation of the ERN (Nieuwenhuis et al., 2001).

Feedback-related negativity (FRN)

The FRN was first discovered in a time-estimation task where participants had to push a button a second after a signal. A feedback stimulus told the participants whether the estimation was good or wrong (Miltner et al., 1997). The resulting FRN is a negative deflections seen at the difference wave (incorrect-correct feedback). This results suggest the FRN is produced by a system that either involves error detection or the use of error information for avoiding future errors. The FRN does not seem to differ between the magnitude of losses or wins in a monetary task (Gehring et al., 2002). Later the FRN is shown to be dependent on the expectancy of the reward (Holroyd et al., 2007). The same feedback can be seen as a loss or win depending on context (Holroyd et al., 2004b). In a monetary task have no loss or no gain, can either be a good feedback or an error feedback, depending on what the other options were. When those were all a monetary loss, the no win/loss feedback was seen as good feedback, while when the other option all were gain option, the no win/loss feedback was seen as an error. An overt action or a contingent response (mapped to the stimuli) are not necessary to generate a FRN (Yeung et al., 2005), although the amplitudes were larger when responses were contingent.

ACC activations

A lot of research has been done on the role of the ACC. There is ACC activity in a large variety of task, which can be subdivided into three categories: task where a change in response was needed, tasks with multiple response possibilities and error-trials. Of the first category, the Stroop task (Stroop et al., 1935), where the colour of the ink must be named, is the most famous. More ACC activity has been seen for incongruent trials (word red writen in green) than for congruent trials (word red writen in red) (Pardo et al., 1990) and activition diminishes when task gets overlearned (Bush et al., 1998). Also in the Erikson flankers task (Eriksen et al., 1974) incongruent flankers (e.g. HHSHH) show a higher activation of the ACC compared to congruent flankers (e.g. SSSSS) (Carter et al., 2000). Another well-known task that falls under the first category is the Go/No-Go task. Again higher activation is seen for the

No-go condition compared to the Go condition (Casey et al., 1997). An effect on frequency on ACC functioning was found in a oddball, Go/No-go and response selection task. Independent if an response had to be given or withhold, the ACC activation was larger for the low-frequency events compared to the high-frequency events, while no ACC activation difference between the responses/events where found when all responses/events where equal (Braver et al., 2001). For the second category most experiments used a fluency task. ACC activation is larger when subjects need to link a verb to a noun compared to repeating the noun (Andreason et al., 1995) or generating words starting with a specific letter compared to reading a list of words starting with that letter (Friston et al., 1993). The last category is with the commision of errors. Increased ACC activation for incorrect responses compared to correct responses has been found (Carter et al., 1998)(Picard et al., 1996) and for negative feedback compared to positive feedback (Ullsperger et al., 2003; but see Ridderinkhof et al. , 2004 for a meta-analysis). An fMRI study showed that the ACC is only active either during external and internal errors. In the beginning of learning, ACC activity was during the feedback, while at the end of the learning, ACC activity was just after the response (Mars et al., 2005).

Summary

When looking at the different properties of the negative deflections similarities pop up between the deflections. The no-go N2/oddball N2 seem all to be dependent on the frequency of a particular stimulus/response. An unfrequent stimulus/response elicit a larger No-go N2. Both the No-go N2 and the N200 are influenced by instruction. When emphasize speed over accuracy the No-go N2 and the N200 both increase. The N200 increases when the stimulus induces response conflict (for example incongruent trials in a Erikson flankers task/ Stroop task or a change/stop trials in a stop-signal task). Both the No-Go N2 and the N200 are induced by task-conditions in which a pre-potent response has to be changed. In the No-Go task and the oddball task the most frequent response has to be overcome when a unfrequent stimuli appears. In the Erikson flankers task and the Stroop task the conflicting information induces faster wrong response activation that has to be overcome.

However this cannot be the process behind the novelty N2, as the novelty N2 is seen as an enhancement of the N2 for a equiprobable novel stimulus compared to the non-target and target. Novelty and sequential matching studies found that the N2 increases with the degree of deviation with the targets, therefor the novelty N2 and the N2 found in sequential matching tasks could be seen as a mismatch process. Beside being unexpected stimuli, the novelty N2 is modulated by deviation from the stimuli set. The last class of negative deflections is made when an error is made either know on the response (internal error) or by

feedback (external error). For both the amplitude increases when accuracy is emphasized over speed and when the error is contigent with a response.
The fMRI data follow the modulations that effect the negative deflections. A higher activation of the ACC is seen in response conflict (either change of response or choice between multiple responses) or when errors are made.

In the next chapter I will discuss 3 major models that all are able to unify several negative deflections by the same process, while the ACC in all three models have a different function for the anterior cingulate cortex.

Chapter 3
The Models

From all the results mentioned above three major theories exist about the function of the ACC or the ERN. One of the theories, the conflict monitoring theory (Yeung et al., 2004), is mainly based on the first category of conditions where the ACC is more active, overriding a pre-potent response. The ACC gets a monitoring function to increase cognitive control when needed. Co-activation of multiple conflicting responses is noticed by the ACC which increases cognitive control to solve the conflict. The other theory about the function of the ACC is the error-likelihood model (Braver et al., 2005). Depending on the stimulus properties the ACC is coding for the likelihood that an error could occur. Activation of the ACC again increases cognitive control to influence the response. The last theory is different from the other because it is focussed on the error-related negativities. Although the ACC is given the function for response-selection, it is possible to give other functions to it. According to the theory the error-related negativities are generated by the dopamine system to train the ACC and other structures. Therefor it is called the reinforcement learning theory (Holroyd et al., 2002). In this chapter we are looking at these three theories in more detail. On what assumptions are these models formulated? Are they capable to account for all the findings found above? What kind of predictions do these models make?

Conflict monitoring theory

Cognitive control is a broader term in which reponse inhibition, detection of response conflict and strategic performance monitoring. Another central function of a cognitive control system is dealing with cross-talk in information processing (Allport et al., 1987). All by all, cognitive control is important for normal cognitive processing and to reduce errors (Cohen et al., 2000).

The purpuse of the conflict monitoring (Yeung et al., 2004, Botvinick et al., 2001) is to reconcile the fMRI findings of ACC activity with ERP-experiments on the ERN. As shown above the ERN was formerly linked to error-processing with the source of the ERN in the ACC. Lots of neuroimaging studies show a higher activation of the ACC with response conflict, where multiple responses compete for control of action (Carter et al., 1998)(Menon et al., 2001), task difficulty (incongruent vs. congruent in the flankers/Stroop task) (MacDonald et al., 2000), when an infrequent response is needed over a more frequent one (Braver et al., 2001) and word generation task with lots of valid responses (Barch et al.,

2000). The conflict monitoring theory tries to give an unified account of ERP findings (ERN) with his source localization in the ACC and fMRI findings (increased ACC activity with increased task difficulty).

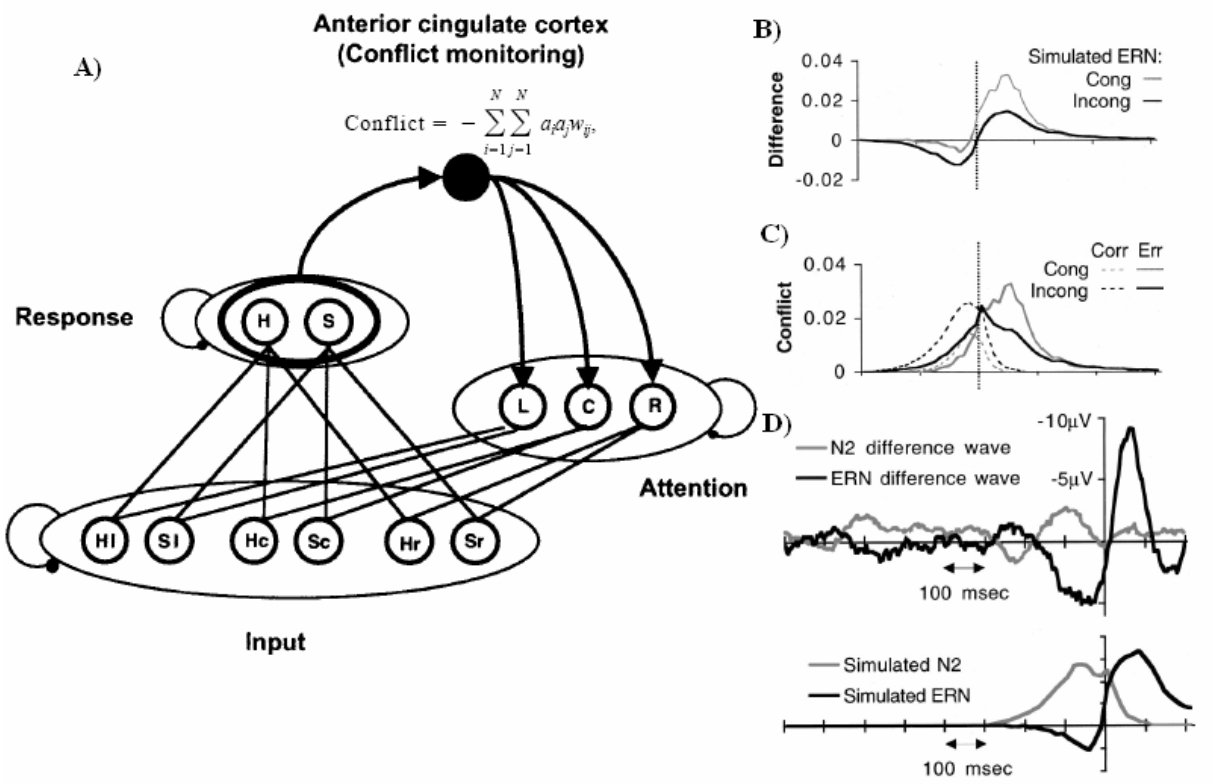


Figure 4: The conflict monitoring theory. A) The computational model modified to replicate finding in the Erikson's flanker task. The model consist of 4 layers of units. The first layer is the input layer, where for each flanker or target there are 2 units. One unit for each response. The unit units are connected with the response unit it is coding for. Within the response layer the response units are inhibiting each other. The third layer, conflict monitor, is activation depending on the energy, the product of activity of all the response units, of the response layer. The conflict monitor can activate an attentional system to modulated the activity of the inputs. B) Simulations of the model indicate that the ERN is larger on congruent trials than on incongruent trials. C) and D) Also on correct trials the model replicates experimental data. A generation of a negative deflection on correct trials with partial errors, activation of the wrong response on correct trials. This is the N200 mentioned above. N2 difference wave is incongruent – congruent condition. ERN difference wave is incorrect – correct trials.

The model used (figure 4A), is a model for the Erikson flankers task, with one central target and one flanker on each side, and consists of 6 input-units, an unit for each possible stimulus (H or S) at each side. This model can be adjusted for modulating other tasks. The input layer is fully interconnected with the response layer of 2 response units, an unit for each response possibility (H or S). The conflict monitor/ACC calculates the conflict by the 'energy', the product of activated units scaled by the strength of the inhibitory connection between them (Hopfield et al., 1982), of the response layer. So when none of the units is active the energy is zero, when only one unit is active the energy is also zero. The only time the energy is getting high is when both units are active and thereby capturing the essence of

conflict. To make the model complete, but not neccessary for following results, the conflict monitoring system can activate an attentional system to influence activation in the input-layer. There are excitatory connections to the next layer and inhibitory connections within a layer, both to all units. The model is clear in the first 2 categories where increased ACC activation was found. When a change in (pre-potent) response is needed or when a choice has te be made between different response options, it is logical both responses are activated. For error-commission and the production of the ERN, it is not that obvious. Two major assumptions are important in this respect. First assumption is that when an error is commited, units/neurons of the wrong response are crossing the threshold for responding before stimulus processing was completed. The second and related assumption is that stimulus processing continues after a response. Together these 2 assumptions are able to see the generation of the ERN as continued processing. Imagine an error was made during a trial. Because an error was made the activation of the wrong response is high and crossed the threshold to respond. Assuming continued processing of the stimulus after an error, the activity of the correct response will increase. During continued processing the activity of both the correct and wrong response is intermediate/high resulting in high energy of the response layer (=conflict). After a correct response, the continued processing will not increase the energy, as it will only increase activity of the correct response, which inhibit the wrong response even more.

Still two major objection were made against the ERN being a product of response conflict. The first one is that a study found that the ERN is larger on errors in congruent trials than errors in incongruent trials (Scheffer et al., 2000). While incongruent trials should produce more conflict. Although counterintuitive the conflict monitoring theory also predicts a larger ERN during errors in congruent trials than incongruent trials, for the same logic as the generation of an ERN (figure 4B). Because for a wrong response the activation of the wrong response is just over threshold for both incongruent and congruent trials, the difference between erroneous congruent and erroneous incongruent trials is due to the difference of the activation of the correct response unit. It makes sense that the activation of the correct response is higher in congruent trials than incongruent trials, because of the conguent flankers that, in addition to the target, activates the flanker units of the correct response. Therefor the conflict, product of activation between correct and wrong response, is higher in the erroneous congruent trials compared to erroneous incongruent trials, resulting in a larger ERN.

The second critism and related to the first one is that experimental data should show an ERN-like deflection on correct trials with high conflict which is not found (Pailing et al., 2000)(Ullsperger et al., 2001). The model indeed predicts a negative deflection on correct trials with high conflict, but predicts that this is prior to the response and not after

(figure4C). So previous experiments have looking in the wrong time window to see this negative deflection. So Yeung et al. (2004) tested this prediction and indeed found a response-locked negative deflection, called N2, prior to the response on correct trials (figure 4D, N2 difference wave: incongruent correct – congruent correct). The ERN and the response-locked N2 on incongruent trials show the same scalp distribution suggesting the same neural source, especially when the stimulus-locked N2 and ERN also have almost identical best fit dipole and scalp distribution.

So this simple computational model is able to account for most of the negative deflections. The No-Go N2 and the N200 are a product of coactivation of both responses in the response layer during stimulus evaluation and response selection. The ERN is due to the idea that only after errors continued stimulus processing is producing conflict in the response layer. Only the FRN is hard to explain by the conflict monitoring theory, because feedback isn't inducing any (response) conflict.

In addition they showed a way in which the conflict monitoring theory can be coupled with error detection. The conflict monitoring theory predicts that the ERN is linked to making errors due to post-response conflict after an error. With a small addition to the conflict monitoring theory the ERN can be signal to an error-detection process. Instead that the ERN is an output of an error-monitoring system the ERN can be used as an input. If response conflict is large after a response, then an error has occurred. A simple accumulator of ACC activity can perform an error-detection process.

Reinforcement learning theory

A very influential model of an error-processing theory is the reinforcement learning theory (Holroyd et al., 2002). The first two major assumptions of the model is that the ERN is part of an high level error-processing system that is generated by the ACC. The first assumption is based on the lots of different error commission experiments have generated the ERN (see ERN above), while the second assumption is based on several dipole localization and fMRI studies (Dehaene et al., 1994)(Braver et al., 2001) and neurophysiological evidence of error-recognition units in the monkeys anterior cingulate sulcus (Niki and Watanabe, 1979)(Gemba et al., 1986). The second set of assumptions is that the mesencephalic dopamine system carries predictive error signals and that these signals can be used in other parts in the brain for reinforcement learning. The predictive error signals are found by a set of experiments that show that dopamine neurons show a positive phasic dopamine response when the outcome is better than predicted, while a negative/suppression of dopamine response when the outcome is worse than expected (Ljungber et al., 1992)(Hollerman et al., 1998). This error signal, also called temporal difference error (TD-error), can be used by other areas to adjust associative strengths

(Schultz et al., 1995). The third set of assumptions couples the generation of the ERN in the ACC with the mesencephalic dopamine system. Neurons in the anterior cingulate sulcus project to other motor areas (Dum and Strick, 1993), suggesting a role of the anterior cingulate sulces as a system that puts motor intentions into action. This idea is strenghtened by the input of the limbic, orbitofrontal, amygdala and prefrontal cortex to the ACC (Morecraft et al., 1998), for emotional and motivational inputs to be able to affect the motor output. Moreover ACC activation is highest during the early phases of learning, while it is diminished when the task gets overlearned (Jenkins et al., 1994)(Bush et al., 1998). In monkeys ACC neurons are activated when the monkey learns the sequences of movements that result in a reward, while activation is absence when the sequence was learned (Proyeck et al., 2000). Finally ACC neurons respond on positive and negative rewards but also on the conditioned stimuli (Nishijo et al., 1997). This coupling between reward and stimuli in the ACC are driven by the mesencephalic dopamine system (Porrino, 1993). These assumptions lead to the reinforcement learning theory of ACC functioning.

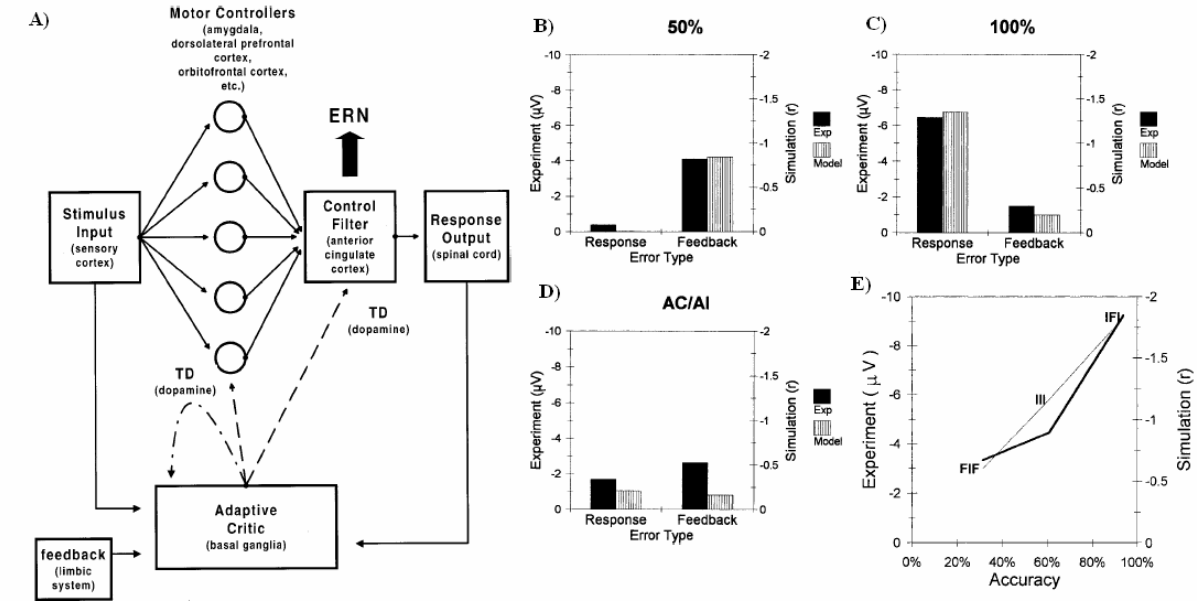


Figure 5: The reinforcement learning theory. A) The computational model. The anterior cingulate cortex (Control Filter) is filtering input from several motor controller that each want their responsee been executed by the responsee output. An efference copy and feedback activate the adaptive critic, that reacts by a temporal difference signal (TD). A temporal difference error, that signals when an outcome is better or worse than expected, is able to weaken or strengthen the connection between the stimulus input and the motor controllers and the connections between the motor controllers and the control filter. In this way the control filters learns to give the right motor controller access to the responsee output. B) When positive and negative feedback was given randomly, the responsee didn't elicit a ERN while the feedback did elicit an FRN. C) A condition where responsee and reward are mapped with 100% validity, there is an ERN but no FRN. D) When every responsee is either correct or incorrect, no ERN and no FRN are elicit. B)C)D) These results suggest big dependency of the ERN and FRN on expectancy. In the 100% condition (C) the outcome is known on the responsee, so the feedback can be expected. On the 50% condition (B) the responsee is not mapped to an correct or incorrect responsee, so no error can occur. E) A correlation between amplitude of the ERN and the accuracy in a modified flankers task. In other words, a larger ERN was found in condition where errors were unexpected.

The model (figure 5A) consists of stimulus input, motor controllers, the ACC, a response output unit and an adaptive critic. Motor controllers are systems that want to exert influence on the response output, but are semi-independent and in parallel. Motor controllers could have different 'ideas' of response output to deal with the stimulus input (e.g. go for direct reinforcement or wait for delayed reinforcement). The ACC is the filter that weights the various 'ideas' of the motor controllers and sends the appropriate response to the response unit. Herefor the ACC needs to learn to recognize, via the mesencephalic dopamine system, which controller is the appropriate controller. The temporal difference-error signal (TD-error send by the mesencephalic dopamine system trains the ACC to select the right response. The TD-error signal can also be used by the motor controllers to adjust there 'ideas'. To test their model they ran two experiments combined with a simulation of the model. The first experiment was a probabilistic learning task. Two of the six stimuli were mapped to one response (one to the left and one to the right button) which gave positive feedback and the other response gave negative feedback (100% mapping). Two other stimuli it did not matter which button was pressed, the feedback was always random positive or negative (50% mapping). The last two stimuli it also did not matter what button was pressed, one stimulus always gave negative feedback and the other always positive feedback (always correct/always incorrect (AC/AI)). As predicted by the model and seen in the experiment the 100% mapping showed a ERN more response-locked, the 50% mapping a ERN more feedback-locked and on the AC/AI a small ERN both response-locked and feedback-locked (figure 5BCD). The model learned the stimulus responses associations. An error in the 100% mappings was known to be an error when the response was made. Therefor the ERN is large just after the response, while in the 50% mapping the positive/negative outcome was only known after feedback, so the ERN is large just after the feedback. An interesting result was found in the second experiment. In a modified flankers task, where one of the two possible targets (S & H) was more frequent (80% vs 20%) while the two possible (S & H) flankers on each side remain equiprobable, with four conditions (frequent compatible (HHHHH), frequent incompatible (SSHSS), infrequent compatible (SSSSS), and infrequent incompatible (HHSHH) or vice versa) the ERN was larger on frequent incompatible than on the infrequent conditions and correlated with accuracy (figure 5E). This result implicates that the amplitude of the ERN depends on whether an error was expected or not, given a larger ERN when the error was unexpected. On the frequent incompatible accuracy was real high (93%), so an error wasn't expected, while one the infrequent incompatible the accuracy was very low (31%) and errors are more likely to happen. So the model's data fits well with some experimental data on the ERN. An addition to the first model, Holroyd et al., (2005) implemented more specific the way an error is detected by the adaptive critic (in there article it is called the monitor module). In the monitor module conjunction units are activated by a combination of stimulus

properties and activation of the response units. This conjuction units is has an affective value that determines the temporal difference error. This extended reinforcement learning model is capable of replicating the fast relative timing of the ERN after error commission, the variation of RT in the modified flankers task between condition and post-error slowing effects that were not able to with the original reinforcement learning theory. The reinforcement learning theory is explicit what and how the ERN is produced, resulting in concrete options to falsify the theory. But the model is not mentioning any stimulus related negativities that occur before the response. Therefor the model only explains a limited amount of negative deflections found in the ACC. Are the other negative deflections generated by activity intrinsic of the ACC? Or is there a way that this model is capable of integrating the other negativities? One possible venue for integrating these other negativities is by a phenomena that are called 'partial errors' (Coles et al., 2005). Partial errors are covert activations of the wrong response on correct trials. These can be measured by using electromyography (EMG) (Vidal et al., 2000). EMG is measuring the electric activity of the muscles, which directly reflects activity of the motor cortices (Burle et al., 2005). The ERN that is produced by partial errors is of the same amplitude then an ERN of a full error (Carbonell et al., 2006). This is in line with the discrete on/off conjunction units in the modified model (Holroyd et al., 2005). The ERN of a partial error might be capable of correcting the erroreous response before it is executed (Burle et al., 2008). However negative deflections on correct trials have also been found without incorrect EMG activation (Vidal et al., 2002), suggesting that they are generated by a process other than error detection.

Besides speeded-responses tasks the model is also capable of reproducing ERN's in tasks were an erroneous response is not clearly defined (Holroyd et al., 2008a). In a Herrnstein decision making task, the value of the response depends on the your response history (figure 6AB) (Herrnstein et al., 1997). The model was able to replicate the subjects behavior (in function 1 responding at 75% hand 1; in function 2 responding (almost) exclusively with hand 2). The results of the difference in ERN amplitude (figure 6CD) shows that ERN amplitude is sensitive to subjective values of the subject to certain responses. In function 2 the ERN of hand 1 is larger than for hand 2, suggesting that hand 2 was the best choice (what it is indeed). But the FRN of hand 2 is larger than hand 1, indicating that the reward of hand 2 was compared to hand 1 a more negative outcome than expected. This fits the function. At every point in the function the reward is bigger for hand 2 than hand 1, but picking hand 2 more often will reduce the reward, while picking hand 1 more often will increase the reward. So everytime hand 1 is chosen the reward will be higher than expected, while everytime hand 2 is chosen the reward will be lower than expected. In function 1 going away from the 75% choosing hand 1 is resulting in a decrease in reward and expected reward in both ways. This indifference is reflected in no difference in the FRNs. Also no difference

between ERNs was found for hand 1 and hand 2 in function 1, what fits as there is no difference in reward at 75 % hand 1.

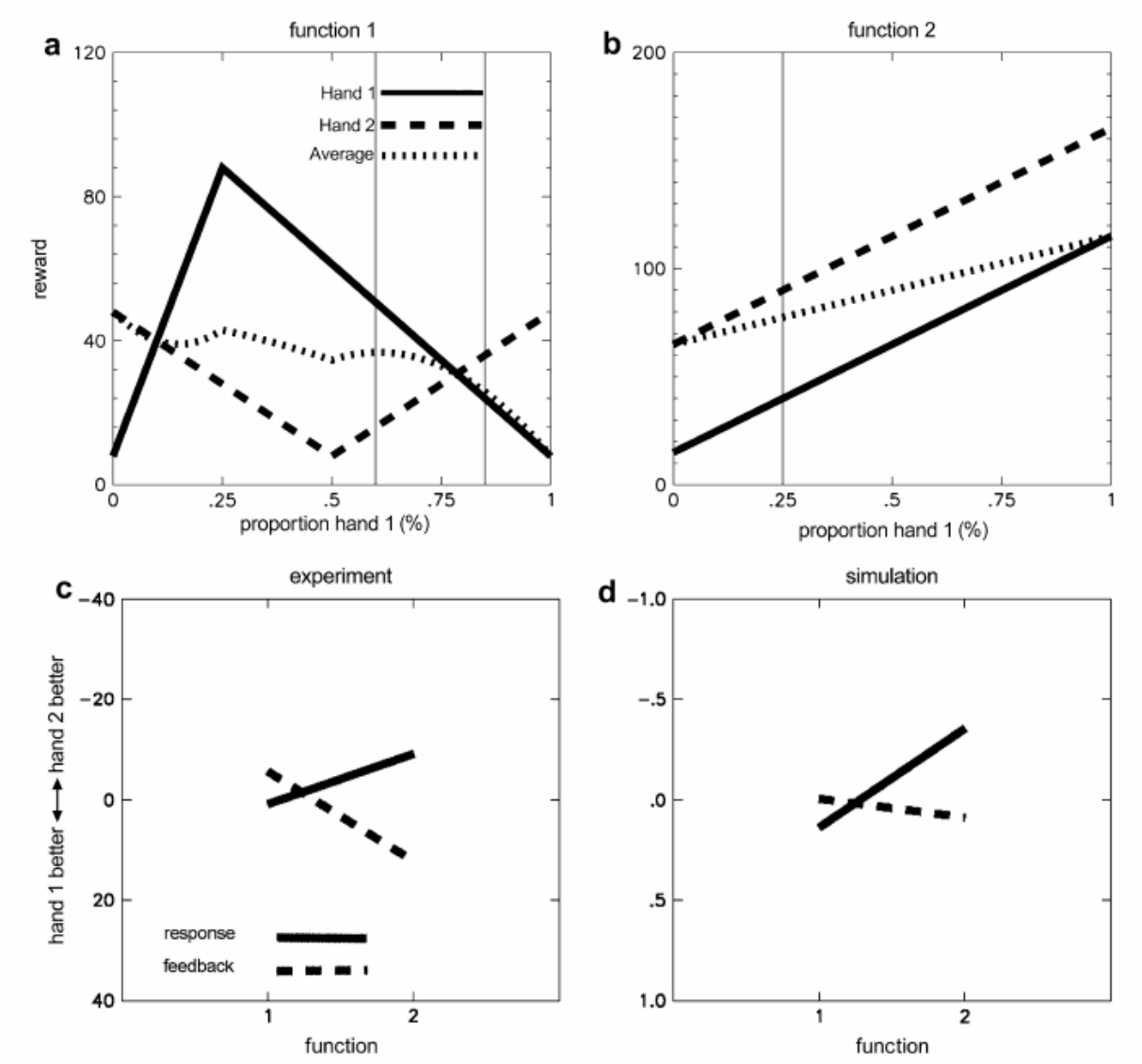


Figure 6: The Herrnstein task. AB) Two different functions that determine the reward depending on the reward history. In function 1 (A) subjects are picking hand one 75% of the times. The rewards are the same for either hand. In function 2 (B) subjects are picking exclusively hand two, although only picking hand one is optimizing reward gain. CD) Difference in the ERN and FRN between the two hands during function 1 and 2 during experiment and simulation. C) No differences in the ERN and FRN in function 1 as both have same expectancy and reward gain, while the subjects had a larger ERN for hand 1 and a larger FRN for hand 2 in function 2. At the responsee the expected reward was higher for hand 2 than for hand 1, which is according to function 2. But at the feedback the reward for hand 1 was larger than expected, while the feedback for the reward when picking hand 2 was smaller than expected. Keep in mind the reward on hand 2 was still bigger than the reward for hand 1.

One problem with difference waves (correct trials minus error trials) used in the ERP-research is that a certain ERP component (in this case the ERN or FRN) can be due to modulations on correct trials but also on error trials (Luck et al., 2005). By using a related negativity also generated by the ACC, the question whether the ERN/FRN is due to a

modulation on error or correct trials might be solvable (Holroyd et al., 2008b). They used a time-estimation task to elicit an FRN in a hard condition (75% errors) and an easy condition (25% errors) and an oddball task (25% odd target). First they validated that the FRN and the N200 where the same component by scalp distribution and same ERP-component in latency and amplitude (although small deviation/attenuation of the peaks due to motivation/stimulus processing) (Holroyd et al., 2004c). If the FRN is a modulation on error trials, the difference wave between infrequent correct and oddball trials is relative flat, while the difference wave between infrequent error and oddball trials show negative deflection. If the FRN is a modulation on correct trials, the difference wave between infrequent error and oddball trials is relative flat, while the difference wave between infrequent correct and oddball trials show a positive deflection. The latter positive deflection was found an called the feedback correct-related-positivity (fCRP). These results suggest that the N200 is elicited by task-relevant stimuli in general, while the fCRP counteract the N200 when a task-goal has been reached. Whether the fCRP inhibit the process that is generating the N200 or is an seperate process that just cancels the N200 in the ERP has to be found out. A serie of experiments found that the N200 and the FRN can be dissociated from each other (Baker et al., 2011). In the first experiment looking for the source of the FRN, they accidently found that in there task conditions that the FRN was delayed by +/- 100 ms and a N200 could be seen on correct trials. A trial consisted of a fixation cross, than a responses that was cued in previous trial and a feedback stimulus coding for reward/no-reward and cued which response was need for the next trial. It was suggested that the delay of the FRN was due to the complexity of the feedback, as it coded for reward feedback and cued action for the next trial. Seperating feedback and the cue for next action, should fasten evaluation of the feedback and a normal FRN should again be seen. Indeed when the cue for the next action was presented before the response in stead of the fixation cross and only reward feedback after the response, resulted in a normal FRN. But suprisingly when the trials consist of fixation cross, decision, cue response next trial and reward feedback several combinations of cue response and probability of reward give rise to different deflections. The feedback stimuli after an infrequent cue when the reward was frequent is eliciting a positive deflection in stead of a FRN, while the feedback stimuli after an infrequent cue when the reward was unfrequent did elicit no special things in the difference wave. Why is this? In all 4 cases there is no indication of a fCRP on the reward trials and the positive deflection is due to a larger negativity on reward trials than no-reward trials. Why an fCRP isnt there and why there is a larger negativity on the reward trials is still suggestive. At least this might explain why there are ERN-like negativities found after a correct response (Vidal et al., 2000) (Suchan et al., 2003).

Although the model started as a model for explaining the ERN and the FRN being generated by the mesencephalic dopamine system, the model eventually investigated the

relationship between the FRN and the N200, to figure out if a negative deflection on error trials or a positive deflection on correct trials was responseible for the FRN. This resulted in a fCRP, a positive deflection on correct trials that counteracted on the N200, which is though be elicited by task-relevant stimuli in general and modulated expectancy. So in a general task trial a task relevant stimulus is presented, which is generating a negative deflection (N200) in the ACC. When responding correctly a positive deflection is counteracting the N200, coding a task goal is achieved. This positive deflection is absent in error trials, resulting in the ERN or FRN. The modulation of expectancy can explain the No-go N2 and the oddball N2. Still a increase of the N200 for incongruent trials in the Erikson's flanker and Stroop task is harder to explain, because in the classical tasks incongruent and congruent trials are equiprobable. Still the model is not able to model the N200, so there is no explanation yet why expectancy modulates the N200. Again the novelty N2 is hard to explain.

Error-likelihood theory

The third model is the error-likelihood theory model (Braver et al., 2005). This model suggest that the ACC, after training, responds to the error-likelihood of a particular input configuration. The error-likelihood is in several ways the same as the conflict monitoring theory. In both theories the ACC produces a signal to increase cognitive control to influence the response selection. The reason why the ACC is active is different between the two theories. In the conflict monitoring theory the ACC is getting more active due to cross-talk, while in the error-likelihood it is because some stimulus properties are associated with a larger error-likelihood. This assumption is based mostly on clinical studies concerning a hypo- or hyperfunction of the ACC. Substance abusers show an unique hypofunction of the ACC compared to controls, which is accompanied by tendencies for more risky behavior despite negative consequences (Fishbein et al., 2005). This result fit with the idea that the ACC is associated with error avoidance (e.a. more activity of the ACC resulting in more cognitive control). An hyperactivity of the ACC found in obsessive-compulsion disorders may lead to an excessive effort to avoid mistakes (Hajcak et al., 2002). Another studie found more ACC activity when subjects were avoiding to engage in a task than at actual error commission (Magno et al., 2006). All these results suggest that the ACC is important for risk/error avoidance in decision making. This led to the following model.

The model consists of a layer of ACC cells, some input units, an error-unit, a control unit and response units (figure 7A). The ACC units were adaptive units, meaning that the weight increases between the stimulus specific input and the unit when both are active on an error trial/when error signal arrives at ACC. Beside being adaptive, ACC units were also competitive, meaning that during an error trial/when error signal arrives at ACC the unactive units decrease they weight with the active stimulus specific input. Together with global lateral

inhibition to other ACC units and lateral excitation to near ACC units, the ACC layer after training consisted of clusters of ACC units reliable coding error-likelihood for a specific stimulus configuration. This ACC layer sends a control signal that inhibites the response layer resulting in increased RT. The same as in the reinforcement learning theory the error signal is produced by phasic suppression of dopamine (Schultz et al., 1995).

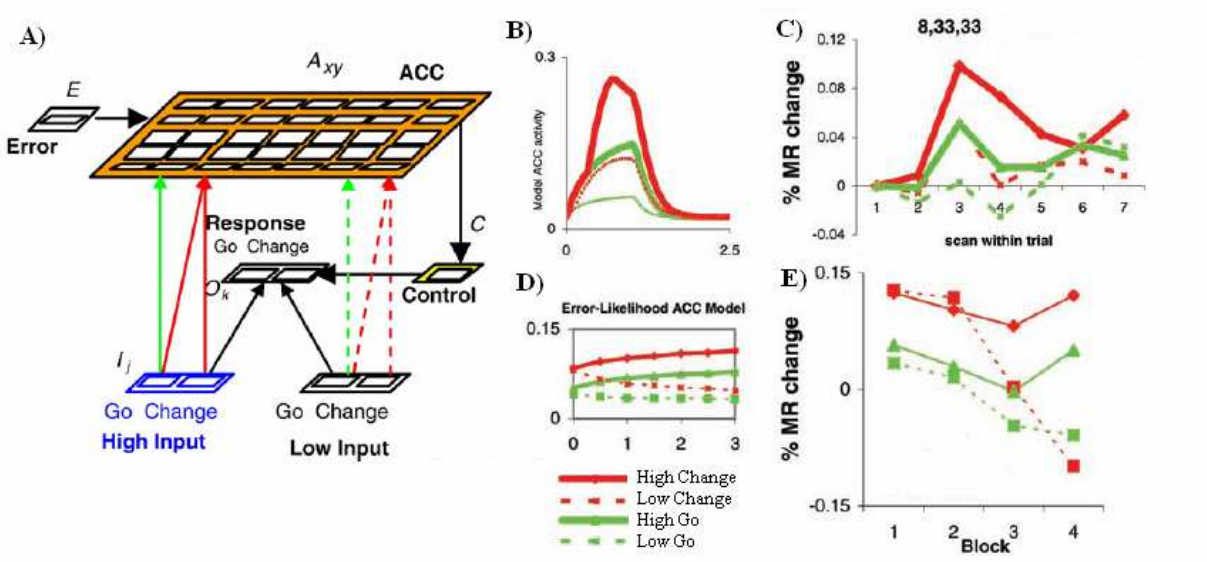


Figure 7: The error-likelihood model. A) The computational model. The ACC is a array of cells coding for the error-likelihood of a specific stimulus configuration. The stimulus configurations all activate the ACC, which according to the amount of activation activate a responsee unit that inhibit the responsee-layer, so it takes longer for a responsee unit to reach the threshold for execution of the responsee, thus increasing the probability of a correct responsee. When an error occurs an error signal strenghten the connection between activated ACC neurons and the activated stimulus configuration, while weakening the other connections. During training more ACC neurons will respond to stimulus configuration related with higher error-likelihood. B) The error-likelihood effect. The error-likelihood effect is an increased activation of the ACC for stimulus configurations (High/Low) that are related to different error-rates. C) Error-likelihood effect validated by experimental data. D) The change in fMRI signal due to stimulus presentation differ in the beginning and end of the experiment. When the stimulus configurations are not related to error-likelihood (Begin of experiment) the Change trials induce have higher change in signal, because of error-signal. When stimulus configurations are associated with error-likelihood the High trials should have a bigger change in signal than the Low trials. E) This is validated by the experimental data.

They tested the model with a change signal task, a variant to the stop-signal task. Either a blue or white arrow pointed to left or the right. The subjects had to response depending on the orientation of the arrow (left index finger for a left arrow; right index finger for a right arrow). After a variable change signal delay (CSD), which was displayed before the response RT, a larger arrow pointing in the other direction could be displayed (33%) and the subject had to change his/her response. For long CSDs errors were made more frequent, the high error condition (50%), than for short CSDs, the low error condition (4%). Using this task both errors and response conflict can be dissociated. The model predicted an error-likelihood effect, larger ACC activity when the likelihood of an error increased. In this task it means an

increase in activity for the High-Change compared to Low-Change condition and increased activity for the High-Go compared to Low-Go condition (figure 7B). This is exactly what they found (figure 7C). As the ACC need to learn the associations through errors another important prediction could be made; the change in ACC signal is larger for change trials (either high or low) compared to go trials (either high or low) in the beginning of the experiment, while in the end of the experiment the change in ACC signal should be larger for high trials than low trials (figure 7D). These predictions are a development from learning from errors on high change trials to the error-likelihood when a blue arrow appears. As predicted the low change trials produce a much smaller BOLD signal than the high change trials (figure 7E). Beside an error-likelihood effect further studies revealed other effects that were predicted by the error-likelihood model. A study (Brown et al., 2007) looked at the consequences that follow an error. Greater ACC-activity has be related to more normative decision-making and less risk seeking (Paulus et al., 2006). For risk aversive behavior not only the chance that an error occurs is important. Equal as important are the consequences that following an error. Using colored cues subjects knew whether the error-likelihood was high and/or the error-consequences were high. Besides again finding an error-likelihood effect, they also found elevated ACC activation levels for high-consequences-low-error-likelihood condition compared to low-consequences-low-error-likelihood condition. They called this the risk expection effect. Because traits like risk-aversion are different between subjects these difference might be reflected in ACC activity. Subjects were divided in a high gambling and low gambling group according on a questionnaire that measures individual differences in risk aversion (Weber et al., 2002). These different group indeed showed very different activities in ACC activity between task conditions. The error-likelihood effect and the expected risk effect were completely absent for the high-gambling subjects. These big individual differences might be the reason why one study wasn't able to replicate the error-likelihood effect (Nieuwenhuis et al., 2007). What was a suprising result is that the high-gambling group has a bigger "conflict effect" (Change correct – Go correct) than the low-gambling group. A follow-up study has showed that this contradictionary result can be explained by just one parameter in the model, the learning rate when an error response (Brown et al., 2008). In the beginning of a certain task, cells of the ACC will respond weakly to all kind of input. After learning, cells of the ACC will preferentially respond to certain cues/condition, with more cells for the cues where the error-likelihood is high compared to low. The model with a lower learning parameter just takes more trials for the cells to differentiate between conditions, but in a real brain activations, connections and error signals are not that strict. Adding a forgetting mechanism, where the cells lose there preference for firing to certain stimuli and also to the other condition, the model might get an intermediate form. So the higher 'conflict effect' in the high-gambling group could be due to

less specificity in the ACC neurons. Althought the response of each neuron might be smaller than in the low-gambling group, a lot more neurons are responding than in the low-gambling group, resulting in a higher overall activity of the ACC. What they also found was that the 'conflict effect' also changed during the stimulations. An increase in the number of trials of the model resulted in a decrease of 'conflict effect' with increased learning (Bush et al., 2000).

Because error-likelihood and response conflict are in most task confounding factors, the error-likelihood model is capable to account for all the fMRI studies of the ACC found in chapter 2. The same is true for the negative deflections that were associated with response conflict, the N200, No-Go N2 and the N2 in oddball tasks. Beside the ability to reconcile all the results from fMRI and ERP studies related to conflict, it can also account for the ERN and the FRN in the same way as the reinforcement learning theory. As with all the above mentioned theories, the novelty N2 is not mentioned and is hard to implement in a model. In the error-likelihood model there might be a modulation because of a smaller response of more ACC neurons to this novel stimuli compared to a larger response of specific group of neurons of a trained stimuli (Brown et al., 2008).

Summary

The conflict monitoring theory, reinforcement learning model and the error-likelihood model all look different at the generation of the ERN and the function of the ACC. The conflict monitoring theory is, compared to the other models, a very simple model that is able to account for the imaging data and almost all negative deflections by a simple computation. Although elegant, the simple model is based on response conflict with some huge assumptions. First of all, how does the ACC knows there is cross-talk, which according to the model is not only related to response conflict but can also be perceptual conflict (Jia et al., 2007) or conflict between memory traces (Rodriquez-Fornell et al., 2004). Even if it is able to 'know' there is cross-talk, than it has to be able to differentiate between cross-talk between neuronal pools that are in conflict with each other and crosstalk between that is needed for the completion of the task, say catching a ball with 2 hands. The reinforcement learning theory on the other hand is a very complicated model with lots of different units neccesary for explaining the ERN, yet has a very defined mechanism for the generation of the ERN and FRN. They suggest that the N200 is elicited by a task-relevant stimuli in general and that a positive deflection (fCRP) on correct trials is responseible for the ERN and FRN in the difference waves. The N200 is suggested to be intrinsic activity of the ACC. Keeping this in mind the reinforcement learning theory is practically the same as the error-likelihood model, when they assume that the N200 is activity signaling the error-likelihood.

In the next chapter we will look at studies that are challenging one of the core assumptions of the theories. After that we well look at some studies that favor one theory over the other. And in the end we summarize our results in the the most plausible function of the ACC and the generation of the negative deflections.

Chapter 4
Testing the models

In this last chapter we are trying to look whether one of the models can be favored over the other. Therefor we start this chapter with studies that challenge one of the core assumptions in one of the 3 models. When such core assumptions are not validated by experiments the model loses a lot of explanatory power. After that we will look at some studies done that may shed some light on the matter and could give a hint to the function of the ACC. We end with the most plausible mechanisms behind the negative deflections.

Comparative studies

In this section we only discuss studies that are comparing the conflict monitoring theory and the error-likelihood model. Because the studies that compare the reinforcement-learning model and the conflict monitoring model are comparing them in respect to differences in the ERN. We discuss these studies in the next paragraph as these studies are challenging the core assumptions of the models. I didn't find studies that directly compare the reinforcement learning theory and the error-likelihood model. This is due to the fact that the whole reinforcement learning is part of the error-likelihood model. Because the reinforcement learning theory doesn't formalize how the selection process in the ACC occurs, comparative fMRI studies between the two are useless.

The first article of the error-likelihood model was comparing the model directly to the conflict monitoring theory. The conflict monitoring theory didn't predict the error-likelihood effect that was found (figure 7C). The conflict monitoring theory should predict that the response conflict did not differ between the High or Low error-likelihood conditions. Beside that a change in ACC activity between blocks (figure 7E), was also only predicted by the error-likelihood model (Brown et al., 2005). Using original conflict monitoring model indeed didn't predict this, cause cues were not implemented in the model. Still it is not hard to image that the high cues allready activate the ACC for upcoming conflict and adjust cognitive control depending on the cue (Gratton et al., 1992). As the cognitive control modulates the input units before stimulus onset, their might be no/very reduced response conflict. Therefor it is hard to dissociate whether the error-likelihood effect is indeed an error-likelihood effect or that ACC activity is associated with upcoming response conflict. The design of this study was not able to rule out the second option.

Another study also tried to control for error-likelihood and conflict by the use of cues in the Stroop task (Aarts et al., 2008), but this study did analyse the change in ACC activity

seperately of the cues and the target stimulus. Aarts et al., (2008) modified a Stroop task that used cues that were either informative or un-informative about the upcoming target, while measuring the response of the ACC with fMRI. Informative cues told with 100% validity whether the target was congruent, incongruent or neutral. This way they could look at the response of the ACC while manipulating error-likelihood, but also response conflict. They found increased activity for informative cues compared to uninformative cues, while activity for congruent or incongruent informative cues did not differ (figure 8a). Beside that the activity of the ACC is lower for informed targets than for uninformed targets and do not differ between congruent, incongruent and neutral informed targets (figure 8bc). These results suggest that the ACC is not modulated by error-likelihood, because cue-related activity of congruent and incongruent is the same, while the likelihood of an error was much higher on incongruent trials. The same effect is found for informed targets. Also the data doesn't follow the conflict monitoring theory. When informent congruent and incongruent targets activate the ACC equally, more anticipatory control should be needed for incongruent trials. Yet this is not what is found. Cue-related activity is the same for congruent and incongruent trials. Turenhout et al., suggested that the ACC has a role for preparatory adjustments/setting control parameters.

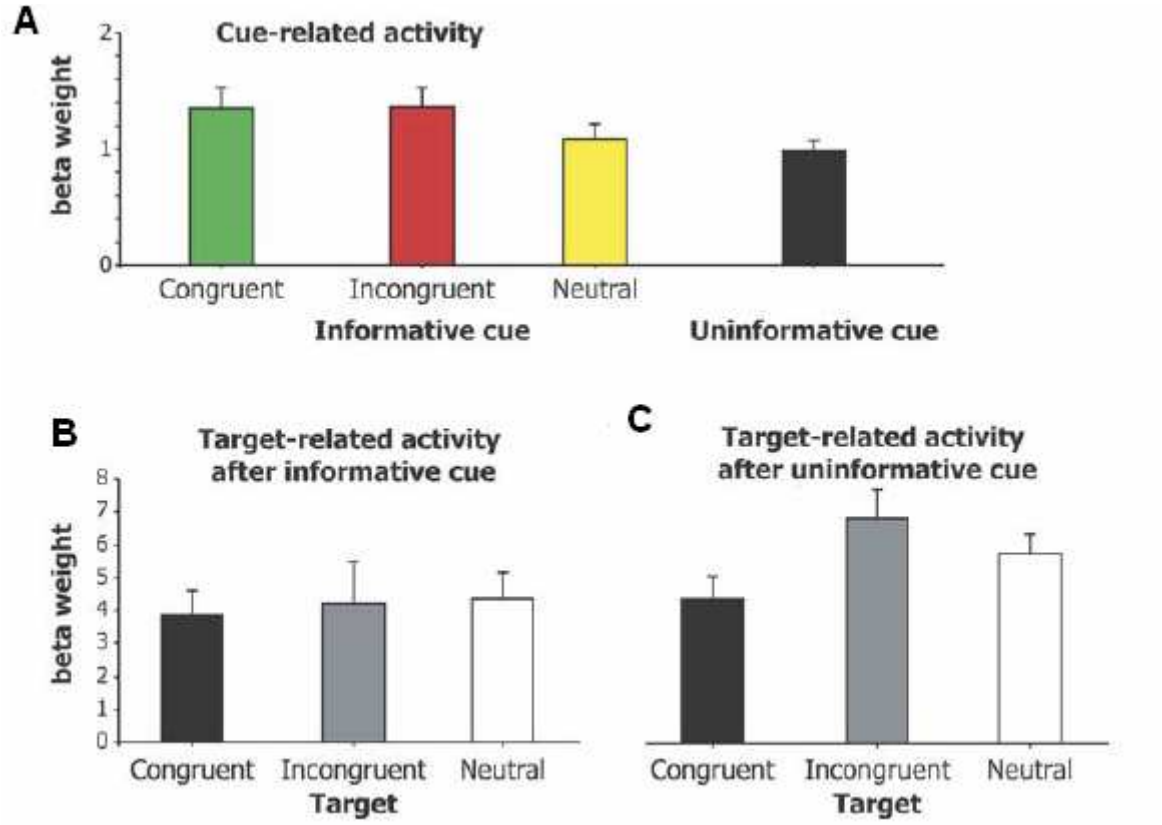


Figure 8: Results of a fMRI study using a cued Stroop task. A) Cue related activity. The ACC showed elevated cue-activity for informative cues compared to uninformative cues, but there was no difference between congruent and incongruent cues. B) Target-related activity after informative cue. There is no difference between ACC activity between congruent, incongruent and neutral targets. C) Target-related activity after uninformative cue. The standard responsee conflict effect. More ACC activity for neutral targets compared to congruent targets and more ACC activity for incongruent targets compared to neutral targets. ACC probably doesn't signal error-likelihood or responsee conflict as the ACC activity is the same for the congruent and incongruent targets are a cue, while error are still more common on the incongruent condition. One could argue that cognitive control is adjusted during the cue, but ACC activity is also the same for the congruent and incongruent cue.

A third article (Brown et al., 2009) we will discuss, is whether the planning of multiple responses are the reason why conflict and error-likelihood effects change during an experiment with the modified change-signal task with predictive cues (Brown et al., 2008). The conflict monitoring theory suggest response conflict for 2 incompatible responses that are active at the same time. However, how does the ACC dissociate between response conflict of the necessary co-activation of two compatible responses. They used a standard and modified Erikson's flanker task and a standard and modified Change-signal task. In the modified versions all cued responses were needed for a correct response. So in an incongruent trials both the left and right button needed to be pressed. The multiple response effect, higher activation when multiple responses are needed, predicted by the error-likelihood model might be the response conflict found in incongruent trials. In the modified tasks multiple responses should increase ACC activity in the error-likelihood model but not in the conflict monitoring theory, as in these conditions the 2 condition are not in conflict. A multiple response effect was found in both task. In the Erikson's flanker task this multiple response effect explained half of the conflict effect, while in the change-signal task it fully explains the conflict effect found in the normal tasks. The result still give room for conflicts effects in the not explained half of the Erikson's flanker task. Although theoretically response conflict can also occur on compatible multiple responses, this not functional for behavior that needs simultaneous responses/movements. This is also not seen in the reaction times which are faster for the modified task compared to the normal tasks, while response conflict is the same, when assuming that response conflict also occurs on compatible multiple responses.

Besides looking at effects that one model can explain, while the other can't, a study tried to dissociate between the error-likelihood model and the conflict monitoring model based on the reaction times for trials (Yeung et al., 2009). They reasoned that trials with a short reaction time have more error-trials, a higher error-likelihood, and are associated with less conflict, while slow reaction times are associated with more conflict but less errors, a lower error-likelihood. According to the conflict monitoring theory the N2 should increase for longer reaction times, while the error-likelihood should predict a larger N2 on faster trials. The N2 followed the prediction of the conflict monitoring theory, although I disagree with the reasoning. They stated that trials with a short reaction time is coupled with a higher error-likelihood. First of all the ACC in the error-likelihood model is activated by stimulus properties that code for the likelihood of an error and not reaction time, that cannot be known at the timing of the N200. Second, ACC activation in both models have the same effect on response selection, namely increased control/inhibition on the response selection to reduce fast guesses. None of these comparative studies are conclusive. Maybe invalidating a core assumption of a theory, can help to falsify a theory.

The core assumptions challenged

One critical assumption of the conflict monitoring theory is that the generation of the negative deflections is due to conflict. Especially response conflict in speeded response tasks, like the Erikson's flanker task. Therefor the amount of response conflict should correlate with the amplitude of the ERN/N200. Another critical assumption found in the other 2 theories, is that the ERN is very dependent on the mesencephalic dopamine system. Therefor changes in the mesencephalic dopamine system should be reflected in the ERN.

The conflict monitoring theory is the most mentioned model of ACC functions because of the elegance that a simple model can explain a lot of phenomena we have seen. It is all based on the fact that the ACC is activated by cross-talk. Combined modeling and experimental studies using a Simons task (Masaki et al., 2007) and an Erikson's flanker (Burle et al., 2008)(Carbonnell et al., 2006) task where used to test this core idea of the conflict monitoring theory. Electromyography (EMG) and exerted force (Carbonnell et al., 2006) has allready been shown to efficiently show covert activation of multiple responses (Burle et al., 2002; Burle et al., 2005) and partial errors (Gehring and Fencsik, 2001); covert activation of the wrong response, while eventual the right response is given. An exerterd force study (Carbonnell et al., 2006) tested the prediction of the conflict monitoring theory, that cross-talk and thus the ERN, between the two responses is larger after incorrect response than on partial errors. Although they found differences in exerted force between partial and full errors, the ERN generated by both was of the same amplitude. Masaki et al., (2007) used the overlap between EMG activity between right and wrong responses as an indication of response conflict and looked whether a larger ERN was indeed found when the overlap between EMG activation of the two responses was higher. They found that in high conflict conditions there was a higher overlap, but the overlap didn't correlate with the ERN. ERNs between the high and low conflict conditions did not differ in amplitude. The same results were found in a study by Burle et al., (2008) using other statistics. They looked at the interaction of the interval between a partial error and the correct response, which is a reflection of conflict, and the N200/ERN. The conflict monitoring model predicts a larger ERN when the interval is short compared to when the interval is long. The experimental data on the other hand showed a larger ERN when the interval was long compared to when the interval was short. These contradictionary results do not favor the conflict monitoring theory. Further analysis showed more interesting results. In a trial-by-trial based analysis they looked at the EMG and primary motor cortices activity for partial errors and correct responses and did not find any overlap between the activities of partial errors and correct responses (figure 9). This suggests that there is no response conflict at all and previous findings of overlap are in fact due to averaging.

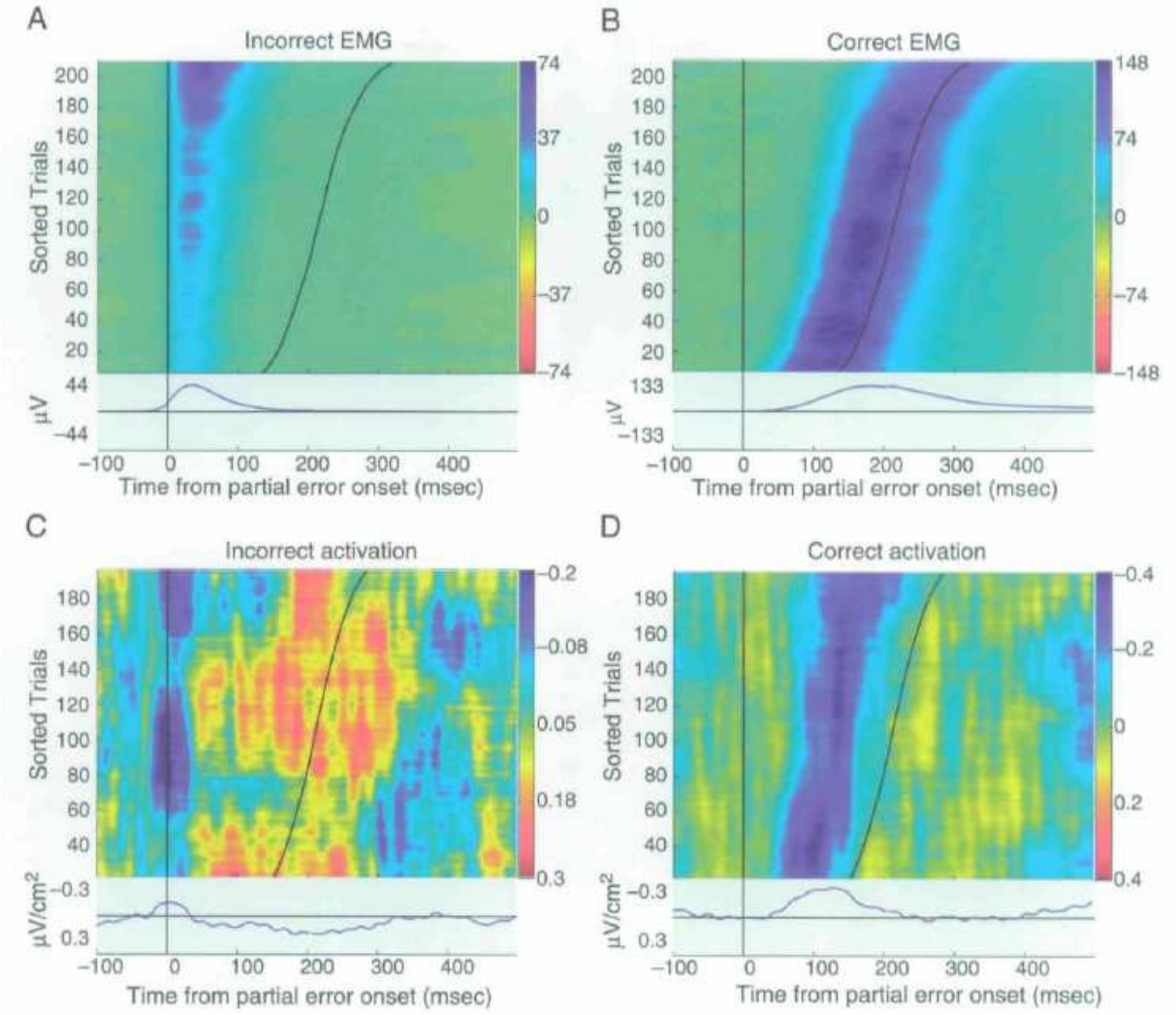


Figure 9: Trial-by-trial EMG and ERP activations of partial errors. Only trials with partial errors were included in the analysis. All trials were sorted on reaction time (the thin black curve). AB) The activity of the incorrect (partial error) and the correct responsee (over responsee) shown in blue measured with EMG. Combining these two graphs shows that the activation of the incorrect responsee does not overlap with the activation of the correct responsee. CD) The same is found with ERP over primary motor cortices.

The other critical assumption is an assumption shared by the reinforcement learning theory and the error-likelihood model. Both state that the ERN and the FRN are both a training signal send by the mesencephalic dopamine system to train the ACC. Therefor the ERN/FRN should change according to changes in the dopamine system. When we first look at the natural development of dopamine in the ACC during a person's life we see that dopamine receptors around the ACC show a large increase in early development (Lambe et al., 2000) and late adulthood (Kaasinen et al., 2000). Dopamine levels show a peak in early adolescence and are later reduced to adults levels (Segalowitz et al., 2009). The ERN seems to follow the same development. There is almost no ERN generated by children between 7

and 12 years old (Wiersema et al., 2007). And from the age of 12 the ERN shows a increase until late adolescence (Ladouceur et al., 2007) (Santesso et al., 2008), while the ERN is decline in elderly people (54-80 years) compared to young adults (18-28 years) (Band and Kovk, 2000)(Mathewson et al., 2005). Also manipulation by drugs that alter the dopamine system should alter the amplitude of the ERN. In a pet study increased ACC activity was found after administration of D-amphetamine, an indirect dopamine agonist (Vollenweider et al., 1998). One study tested the effect of D-amphetamine, the sedative lorazepam and the antidepressant mirtazapine on the ERN (deBruin et al., 2004). D-amphetamine is acting on dopamine, while the sedatives lorazepam and mirtazapine is acting on GABAergic and histaminergic pathways. D-amphetamine had an enhanced effect on the ERN and subjects felt like they were more alert and performed better, although no real enhancement of performance was found after administration. Also the effect of D-amphetamine was a specific enhancement of the ERN, while the N2 and P3 showed no enhancement. Lorazepam reduced the ERN, but also the N200. No modulation of mirtazapine was found. Together the results of D-amphetamine and lorazepam dissociate the ERN and N200 as different processes.

Besides a modulation of a healthy dopamine system, some mental disease have been linked to a non-functional dopamine system. One of them is Parkinson's disease that is characterized by a degeneration of dopaminergic neurons. Both theories thus predict that there are differences between the ERN/FRN between controls and subjects with Parkinson's disease. Indeed an attenuated ERN was found for patients with Parkinson's disease in the Erikson's flanker task, No-go task (Falkenstein et al., 2001) but also on a lexical decision task (Ito and Kitagawa, 2006). A third study (Stemmer et al., 2007) also looked whether the medication reversed the attenuated ERN in subjects with Parkinson's disease. Suprisingly, medicated and non-medicated subjects with Parkinson's disease show the same attenuation of the ERN compared to healthy control subjects. Why did the medication not modulate the ERN? Further inspection between the two patient groups showed that both patient groups had the same performance level/severity of the disease, as assessed by the unified parkinson's disease rating scale (UPDRS) (Fahn et al., 1987). Indicating that the medication did not bring the dopamine levels of patients back to the levels of healthy control subjects but to the level of the non-medicated subjects. It has been shown that dopamine uptake increases with the severity of the disease (Berding et al., 2000). The medicated subjects were in a further stage of the disease than the non-medicated patients. Also an enhanced ERN was found in patients with obsessive compulsion disorder (OCD) (Gehring et al., 2000) and these patients also showed an increase activity of the ACC (Adler et al., 2000). The opposite, reduced ERN and ACC activity, was found in schizophrenic patients (Kopp et al., 1999)(Laurens et al., 2003).

A related assumption is that training-signal the ACC gets from the mesencephalic dopamine system is a temporal difference error. A temporal difference error is a phasic dopamine signal that indicates whether an outcome was worse or better than expected (Holroyd et al., 2002). So an expected outcome should produce a small temporal difference error, while an unexpected outcome should produce a large temporal difference error. By using two different guessing tasks this prediction was not validated (Hajcak et al., 2005). In the first guessing task the subjects had to choose 1 out of 4 doors. A cue in the beginning of the trial indicated whether behind 1, 2 or 3 doors there was a reward. In the second guessing task the subject had to choose 1 out of 4 balloons. During blocks rewards were given randomly either 25%, 50% or 75% probability. Although a distinct FRN in the difference wave, there was no modulation by the expectancy of reward. How so? In a series of experiments Holroyd et al., (2009) tried to figure out why there was no modulation during these tasks. In the first experiment the probabilities were changed to 5% for the unexpected reward and 95% for the expected reward. Yet still no modulation of the FRN was found between an expected or unexpected reward. In the second experiment they suggested that in most FRN studies, subjects had to associate between a stimulus and the probability of a reward. So instead of explicit show the probability, different stimuli were associated with different probabilities. By trial-and-error subjects had to associate the probability of a reward in the trial depending on a certain stimulus. Still these modification didn't show any modulation of the FRN on reward probabilities. In the last and final experiment they thoughed that the missing link was that there is no connection between the response and the feedback that was given, as the feedback in all the previous experiments was given random with a certain probability. In the last experiment they added a constant stimulus-response mappings. Say for one stimulus the left button had a 80% chance of a reward, while the right button gave no reward. Six different stimulus for 80%, 50%, 20% probabilities either the left or right button. After this manipulation there was a clear modulation by probability. It that the FRN is only sensitive to reward probability, but only in a task where there is a optimal response to learn. A follow-up study (Hajcak et al., 2007) did the same experiment as in there first study, but the subjects were also asked how much they expected a reward. An interesting finding was that the modulation of the FRN did follow the subjective expectancy, but only after they made there response. Later modulation of the FRN by a reward prediction error was found (Holroyd et al., 2007).

Single Cell Studies

We will look at single cell recordings done in the ACC. Because most of these recordings are done in the ACC of primates, we have to keep in mind that the ACC in humans might have other functional implications than primates. We will look at several specific activations of neurons during several stages of a trial.

The first study looked specifically at the responses of neurons before stimulus onset (Johnston et al., 2007). In the task, the monkeys had to make a saccade either to the light flash (prosaccade) or away from the light flash (antisaccade). After 30 trials the task conditions switched without instruction. 23% of all recorded neurons showed task-related differences in preparatory activity either for the prosaccade or the antisaccade task condition. The strenght of task selectivity developed during one period of one task condition. The strength of task selective activity was highest and started earliest in the first trials of the block. For prefrontal neurons task selective preparatory activity was stable during a whole block. Also ACC neurons showed strong task selective activity on correct trials following correct and error trials, while PFC neurons only showed strong task selective activity on correct trials following correct trials.

In a good controled study Williams et al. (2004) looked at human ACC neurons. The subjects performed a sequential two-choice selection task. The subjects were instructed for the correct upcoming action (moving a joystick either to the left or right). In 80% of the trials the subjects had to perform the same action as the previous trial for 15 cents (standard-reward trials), in 10 % of the trials the subjects had to change side for 9 cents (reduced-change trials) and in 10 % of the trials the subject ahd to change side for 15 cents (double arrow trials). A significant increase in activity was found in reduce-reward trials compared to standard-reward trials in 32% of all the cells. A comparison with the double-arrow trials, 2 subsets of these neurons showed more activity either for reduced-change trial (32%) or the double-arrow trials (16%), although over the entire sample the activity on reduced-change trials is larger than on double-arrow trials. There is no difference in activity between standard-reward trials and double-arrow trials, suggesting some cells show modulation for switch instruction, but that the magnitude of the modulation is dependent on reward context. The activity during the instruction period was only predictive for the response outcome for the reduced-reward trials. After cingulotomy, removal of the dACC, the error rates for reduced-change trials went from 5% to 64% and for the double-arrow trials from 3% to 28%, while error-rate for the standard-reward trials stayed the same. These finding suggest that the dACC signals for alternative actions, especially when the reward is reduced.

Another monkey study look specifically at ACC activity between stimulus onset and response (Kennerley et al., 2006). Several stimuli were mapped either to the amount of reward, reward probabily or the cost to get a reward. Monkeys had to choose between 2

presented stimuli. Stimulus-responses mappings were very important to choose the 'correct' stimulus. 84% of all the neurons in the ACC reached the criteria for encoding stimulus value in at least one of the decision variables. A lot of the ACC neurons encoded stimulus value for 2 or even 3 variables. After evaluating the value of the response options, the monkey had to make a response. 50% of the neurons in the ACC reached the criterion for encoding of the motor response in any of the 3 decision variables. When comparing the latencies when the neurons reached the criterion for encoding of either stimulus value or motor response, the stimulus value is encoded before the motor response, which is consistent with the notion that the value of the stimuli are needed to make an appropiate response.

Many single cell recordings have shown error-related modulation in ACC neurons. Neurons were found that are sensitive to the degree of reward expectancy (Shidara et al., 2002), ommission of errors (Ito et al., 2003), responding different to rewarding or aversive rewards (Nishijo et al., 1997), code for reward prediction errors (Amiez et al., 2005) or respond more to rewards following a correct response than a passive reward (Michelet et al., 2007). One study used a task where monkeys needed to search for one stimulus out of four that was rewarding (Quilodran et al., 2008). After the rewarded stimulus was found 3 more trials with the same stimulus-reward mappings were done. Therefor one set of trials with the same stimulus-reward mapping had a clear exploration (search) and exploitation (repetition) period. Some neurons showed different pre-response activity between search and repetition periods. 10% of all recorded neurons were inhibited during the pre-response in repetition trials, while a population of 15% of all recorded neurons were activated during the pre-response period of a search trial. Looking at the neurons that show feed-back related activity, 7% had more activity during incorrect and first correct feedback (INC/CO1), 6% were responseive to correct feedback (COR), 22% were response to incorrect responses (INC) and 17% were responses only to the first correct reward (CO1). The last class neurons respond selectively with the discovery of the reward and the shift between search and repetition. The last observation was that 13,5% of the neurons increased there activity after lever press, following the discovery of the reward. No activity was found after feedback in these neurons. In other words, these neurons were reactive to the first reward, after which they reacted to the initiation of the next (surely rewarded) trial and not to the reward itself.

Another study showed cells that signal for movement alternation (Shima et al., 1998). Monkeys were trained to perform 2 different movements after a visual go stimulus. Both movements result in most of the trials to the same reward. After several trials were the monkeys performed the same movement the reward was reduced. After the reduced-reward trial, the monkeys chose 'voluntarily' to perform the other movement and again got the standard reward. Four types of neurons showed activity between the reduced reward and the subsequent changed movement, that was not seen between to trials without alternation in

movement. Some had activity only just after the reduced response, while other had activity builded up and peaked at movement initiation. Also for most of those neurons the activity was specific for what kind of movement the changed movement is gonna be. Also when a tone signaled the monkeys to change the movement, these signals were not seen. These results suggest that the rACC is crucial for reward-based motor selection.

Summary

The comparative studies that were testing 2 different predictions made by the conflict monitoring theory and the error-likelihood during a specific task, where not exclusively supporting one over the other. The results was not conclusive (Brown et al., 2009) or the assumptions of the experiment has a flaw (Yeung et al., 2009). In the Brown et al. (2005) and Aarts et al. (2008) studies used cues to control for error-likelihood and conflict. Results in the first study was not able to rule out the possibility that cues are activating the ACC for upcoming response conflict, the second study was. What it found was no error-likelihood effect but also no conflict effects, suggesting another function of the ACC compared to the error-likelihood model and the conflict monitoring model. So the fMRI studies were not able to dissociate between the conflict monitoring and error-likelihood model, but experiments testing the generation of the ERN where illuminating.

The ERN in the reinforcement learning theory and the error-likelihood model is generated by the mesencephalic dopamine system, while in the conflict monitoring theory by co-activation of two incompatible responses during continued stimulus processing after erroneous responses. A set of studies (Burle et al., 2005) (Masaki et al., 2007) (Carbonell et al., 2006) tested whether the amount co-activation of two incompatible responses related to the amplitude of the ERN. None of these studies found this relationship. One study (Burle et al., 2008) did not even found co-activation of the two response in a trial-by-trial analysis, suggesting that the found co-activation between the two responses is in fact an averaging artifact. On the other hand manipulations of the dopamine system have an effect on the amplitude of the ERN. Depletion by dopamine either by age (Segalowitz et al., 2009) or Parkinson's disease attenuated the ERN (Stemmer et al., 2007), while induction of a dopamine agonist increases the ERN (de Bruin et al., 2004). Thus a large body of evidence is indicating that the ERN is produced by the dopamine system and not by response conflict.

However a dissocation between the N200 and the FRN is found by experimental manipulation (Baker et al., 2011) and also in a drug study (de Bruin et al., 2004), so what is producing the N200. Single cell recordings were able to shed some light on this issue. ACC neurons seem to be active in a larg variety of elements within a trial. First of all, ACC neurons seem to be selective active for a certain task-condition in a preparatory period (Johnston et al., 2007). The ACC seem to be important for changing stimulus-response mapping, induced

by errors or cues (Williams et al., 2004). During stimulus processing ACC neurons seem to code for expected reward related to the stimulus and respond according to the reward expectation (Kennerly et al., 2006). After responding the ACC neurons were modulated by incorrect responses and unexpected reward (Amiez et al., 2005). And ACC neurons signal an adjustment in behavior after unexpected reward (Quilodran et al., 2008) and errors (Shima et al., 2006).

How do all the results found in this chapter and previous chapter can be unified? In the next chapter I will wrap all results in one idea.

Chapter 5
An unified function

ACC Function

As seen in the previous chapter the ERN is produced by a reward prediction error by the mesencephalic dopamine system. Also several studies found that the FRN is modulated by a reward prediction error. The reinforcement learning theory (Holroyd et al., 2002) is the theory that first suggested this and unified the ERN and the FRN as the same negative deflection depending on the stimulus-responses-reward mappings. After comparing the FRN to the N200 (Holroyd et al., 2008b) to solve the inverse problem (Luck et al., 2005), whether the FRN is a modulation on error trials or on correct trials, it seems that the ERN and FRN are due to a positive deflection (fCRP) on correct trials rather than an negative deflection on correct trials. By accidence a experimental manipulation increased the latency of the fCRP and showed the N200 (Baker et al., 2011). Together with a different modulation by d-ampethamine (selective enhancement of the ERN, but no effect on the N200) and lorezepam (attenuation of both the ERN and N200), suggest that the N200 is generated by another process than the ERN and the FRN. But both generated by the anterior cingulate cortex.

It might be that the other negativities are due to activation of the ACC because of percieved response conflict but this seems very unlikely because (1) studies are challenging whether there is actual response conflict in the motor cortices, (2) the conflict monitoring theory is not capable of explaining the error-likelihood effect, risk expectancy effect and the multiple response effect based on response conflict of multiple incompatible response activations and (3) it is hard to reconcile how a structure that notice response conflict is needing a training signal by the dopamine system.

The error-likelihood model suggest that the process responseible for the N200 and No-go N2 is a process indicating the likelihood for an error for a certain stimulus configuration (Braver et al., 2005). But not all the studies agree with this view. First of all the discovery of an N200 after a feedback besides an FRN does not match the error-likelihood model (Baker et al., 2011). Why should a feedback elicit an error-likelihood independent of an error signal? Also an fMRI study (Aarts et al., 2008) did not find increased activation of the ACC for an incongruent cue than for a congruent cue, although the error-likelihood is much larger for cued incongruent trials than cued congruent trials. Some of the single cell studies don't fit with the error-likelihood model either. Why should cells selective for the current task representation be active during a preparatory period (Johnston et al., 2005)?

Why should someone with after a cingulotomy have such a difficulty with changing it behavior (Williams et al., 2004)? Why should the ACC contain cells that after an reward prediction error remain active till the next movement (Shima et al., 1998)? These results suggest that the ACC is performing another function. The ACC function seems to be to guide/select actions dependent on the expected value of the reward (Rushworth et al., 2004). This is mainly based on the single cell recordings. Together all the single cell studies found effects related to the selection of an action either in a preparatory period, where the subject can anticipate the correct response, or during stimulus processing. Subjects are having problems changing there behavior when the ACC is gone or inactive. And the selection of action is responseive to a reward prediction dopamine signal, that could be able to change stimulus-value mapping and stimulus-response mappings.

To summarize, these results suggest that the ACC is responseible for response selection, as it contains stimulus-response-outcome mappings. Depending on the expected value of reward the stimulus-response mapping system is chosen the response that will gain the most reward. Reward prediction errors are used to change the mappings when an outcome is more or less than expected. But can this action-selection mechanism explain the negative deflections and fMRI studies we have found so far? Before I argue that it can, I need to stress that the relationship between action potentials and LFP, especially gamma, is crucial. Because LFP gamma oscillations are way better predictors for the BOLD (Logothetis et al., 2004) signal than action potentials are (Logothetis et al., 2003), explaining the fMRI by a action-selection process, mostly based on single cell studies, is suggestive.

No-go N2, Oddball N2, N200 and response conflict

The negative deflection found on no-go trials in the Go/No-go task and the targets in the oddball task was foremost explained by an expectancy effect (Nieuwenhuis et al., 2003). The more unexpected the target in the oddball task or the No-go stimulus was the higher the N2. Also an enchancement was found when speed was emphasized over accuracy (Jodo et al., 1992) and an overt response was given compared to an covert response (Bruin et al., 2002).

The N200 that is found in speeded response task with conflicting stimuli, like the Erikson's flanker task, the Stroop task and the stop-signal task. Again the N200 is larger when speed is emphasized over accuracy. The amplitude is larger for unsuccesfull trials compared to succesfull trials (Boxtel et al., 2001), larger for slow trials compared to fast trials (in the Erikson's flanker and Stroop task) (Yeung et al., 2004), larger for a long stop-signal delay compared to a short stop-signal delay (Ramautar et al., 2006). In the action-selection view of the ACC the No-Go N2, Oddball N2 and the N200 also relates to response conflict, but different than the conflict monitoring model. Here ACC activity is the planning/co-activation of multiple responses in order to select the correct one, while in the conflict

monitoring model the ACC activity is activated when multiple responses are activated. Becuase there will hardly be any preparatory activation of a response in the Erikson's flanker and Stroop task as in most studies the congruent and incongruent trials are equiprobable, incongruent trials will induce also the response related to the flankers. In the stop-signal task the N200 is generated because the stop signal needs a change in response. The larger N200 when the time between go and stop signal increases could reflect the larger response conflict between the two responses. For the larger negative deflection found for unfrequent responses compared to frequent responses. The response conflict is generated because ACC neurons allready activate the frequent response in the preparatory period before trial-onset. But due to stimulus processing of the unfrequent stimulus the ACC will have to change from the expected frequent response to the unfrequent response, resulting in activation of both responses. When speed is emphasized the preparatory activation of the frequent response is larger to be able to respond faster on stimulus onset.

Novelty N2

One of the negativities was out of the picture almost the entire thesis, namely the novelty N2. As allready mentioned above the novelty research is mainly focussing on the P3a. A positive deflection that is related to shift attention in response to novel stimuli. Another reason is probably that it all of the theories not tried to explain the novelty N2. But in the reinforcement literature I found unfrequent neutral stimuli that are novel or elicit orienting of attention without reinforcing consequences seem to robustly elicity a phasic response in dopamine neurons (Ljungberg et al., 1992). So according to the action-selection view of the ACC the novelty N2 is the No-go N2 plus a modulation by the phasic dopamine system.

Error-likelihood, Risk expection and the Multiple response effect

Studies of the error-likelihood model have shown some effects in ACC activity. An increase in ACC activity has been found when the likelihood of an error increased (Brown et al., 2005). Also increased ACC activity has been found when the big consequences of an error compared to little consequences of an error (Braver et al., 2007). Finally they found a multiple response effect, where they found a larger ACC activity when multiple compatible responses activated (Brown et al., 2009). For the action-selection view of the ACC the multiple response effect is also suggested, as some neurons code for a specific response, more neurons are activated when multiple responses are needed. However the action-selection view of the ACC might explain why there is more activation found in the change-signal task on multiple response incongruent trial than on an standard incongruent trial. During a standard incongruent trial the ACC 'only' has to change/activate the other response and reduce activity of the ongoing response. In the multiple response incongruent trials the ACC

has to activate the other response but also activate the ongoing response. The error-likelihood effect can be confounded with anticipatory activation of the ACC, as mentioned above. When a cue is signaling for a trials with a large error-likelihood (long interval between first stimulus and the change response stimulus). The ACC could anticipate on the upcoming change in response by prepare both responses. When cues were not signaling the error-likelihood but the type of Stroop trial (Aarts et al., 2008), no error-likelihood effect was found on either the cue or the cued target. Congruent and incongruent cues activated the ACC in the same way an more than neutral cues. This could indicate that due to informative cues the ACC could prepare for one of the trials (either congruent or incongruent). This is reflected in the fact that no response conflict effect was found in cued targets, while it was present in targets that were not cued. The action-selection can 'adjust cognitive control' (inhibit responses related to shape/color/positions) reducing the planning of multiple responses. The risk expection effect, more activity of the ACC when consequences of an error are larger, can intuitively be explained that a trial where the consequence of an error are high, subjects do not want a error. Therefor the change responses might be activated in case a change signal occurs. However this is very suggestive.

Conclusion

The action-selection view of the ACC, allready suggested by the reinforcement-learning theory is able to unify the results we found during this thesis. The main components of the ACC in relationship with the negative deflections is that all negativities except the ERN, FRN and the novelty N2 are due to activation of multiple response options or a change in response in the ACC. The ERN and FRN are reward prediction signals that strenghten or weaken stimulus-value mappings and/or stimulus-response mappings depending on a unexpected reward or an error.

Future directions

As we saw there are a substantial number of studies on the ERN and the N200. In the action-selection view the N200 is a result of response conflict that can happen between co-activation of two stimulus-driven response (incongruency effect) or by co-activation where was is an expected response and the other is a stimulus-driven response. These expected responses can be due to the use of a cue or one stimulus being more frequent than another stimulus. One prediction of the proposed model is that an increased N200 will occur when a stimulus signals that an infrequent response is needed, after a cue that signals that a frequent response is needed. Before cue onset the system should allready prefer the frequent response and therefor the 'frequent'-cue will not need a change in prepared response. Another loose end is the novelty N2. Why is the mesencephalic dopamine system producing a reward

prediction error when an novel stimulus occurs? One line of view is that the phasic dopamine signal after a novel positive stimulus is a timestamp to correlate the novel positive stimulus with ongoing behavior (Redgrave et al., 2007). Another line of research regarding the action-selection view of the ACC is to study how other structures (motor controllers (Holroyd et al., 2002)) influence the action-selection process. How to the amygdala, prefrontal, orbitofrontal and other interact within the ACC to influence action-selection? Do all structures influence the action-selection process or is one structure in charge of action-selection in one task and the other in another task? Because response conflict seems to be more of a

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