EVENT RELATED POTENTIAL CORRELATES OF MOVEMENT PRODUCTION AND THE REGULATION AND MONITORING OF ACTIONS

Elektrische hersenactiviteit gerelateerd aan het produceren van bewegingen en de controle en evaluatie van motorische acties

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Introduction

Humans have the ability to interact with the environment by producing voluntary movements and responding to relevant external events. Since human performance is rarely perfect, an important task of the human information processing system also concerns the monitoring of actions (Rabbitt, 1967). In this way departures from required performance are detected and adjustments can be made to eliminate, or reduce, errors.

This thesis describes experiments on the planning, execution and evaluation of voluntary movement. To this end, brain activity in the electro-encephalogram (EEG) accompanying both hand and eye movements are examined.

Paragraph 1.1 reviews the cortical control of voluntary hand and eye movement. The central pathways by which hand movements are initiated differ to a large extent from those mediating eye movements. Therefore, the study of brain potentials for these two movement types can provide additional information on whether the recorded brain activity is movement specific or whether the potentials reflect generic cortical mechanisms independent of movement output.

In **paragraph 1.2** the neural events underlying the EEG are discussed.

Electrical potentials accompanying specific brain functions are generally small and hidden in the ongoing activity of the human EEG. Event related cortical activity can be distinguished from the EEG background by using the averaging technique described in **paragraph 1.3**. Two important types of premovement brain potentials discovered with the averaging method are also presented. These are the readiness potential (RP) preceding self-initiated movements (§ 1.3.1) and the contingent negative variation (CNV) preceding movements made in the context of reaction time experiments (§ 1.3.2). In addition to motor-related activity, the recorded event related potentials (ERPs) typically include brain activity related to non-motor functions like those corresponding to sensory and cognitive processes. The lateralized readiness potential (LRP) measure can be applied to extract movement specific contributions to the ERPs (§ 1.3.3). The LRP has proved to be an important experimental tool in studies on human information processing. One important result from those experiments concerns the LRP based analysis of motor related processing in the so-called flanker reaction task described in paragraph 1.3.4.

In **paragraph 1.4** an overview will be given of ERP components presumed to be correlates of cortical mechanisms involved with movement regulation (motor inhibition) and action monitoring.

Finally, in **paragraph 1.5** the specific research questions of experimental chapters 2, 3 and 4 are presented.

1.1. Cortical control of voluntary movement

1.1.1. Hand movement

Limb movement is subserved by the cerebral cortex through a primary motor

area (MI) and several premotor areas (Fig. 1: top panel). The primary motor area MI located in the precentral gyrus is part of the final common motor pathway. It contains neurons that can activate the muscles necessary for limb movement through projections to nerve cells in the spinal cord. The motor areas controlling hand movement are located on the lateral surface of MI. Cortical motor control exhibits a contralateral organization; movement of the right hand is subserved primarily by the motor cortex of the left hemisphere, left hand movement is controlled mainly by primary motor areas of the right hemisphere. The cortical premotor areas anterior to the precentral gyrus are involved mainly in the planning of movements, although these areas also access the spinal tract directly. Two main premotor regions can be distinguished: the lateral premotor areas on the lateral surface of the brain and the supplementary motor area (SMA) in the medial walls of the cerebral hemispheres (Fig. 1). The lateral premotor areas are involved primarily with selection of movements in response to events in the external environment. These areas play an important role in stimulus-response mapping, i.e., the selection of an appropriate response following a relevant external event. The SMA is involved in the preparation of self-initiated movements and coordination of left and right hand movement. In addition, the SMA is believed to be important for the implementation of more intricate motor programs, like those necessary for making complex sequences of finger movements (e.g. piano playing).

1.1.2. Eye movement

The cerebral cortex also contains areas specialized for the control of gaze. This thesis concentrates partially on brain potentials accompanying saccadic eye movements. These are fast eye movement used to shift the fovea to an object of interest. The fovea is the part of the retina where visual acuity is highest. In the bottom panel of Fig. 1 the main cortical areas governing saccadic eye movements are depicted; the posterior parietal cortex (PPC), dorsolateral prefrontal cortex (PFC: i.e., area 46 of Brodmann), frontal eye fields (FEF) and supplementary eye fields (SEF). Two of these areas, the FEF and SEF can trigger saccades via a direct projection to the brain stem premotor reticular formations, also referred to as the brain stem saccade generator or oculomotor plant, where signals from higher brain centers are translated into specific commands for the extraocular muscles. The FEF located at the lateral part of the precentral sulcus, just anterior to the primary motor cortex controlling hand movement, is concerned most directly with the generation of intentional visually guided saccades. The FEF also projects indirectly to the brainstem saccade generator via the superior colliculus (SC). The SC in the midbrain pons is an important relay station between saccade control signals from higher brain centers and the brain stem reticular formations. The FEF contains three classes of neurons; visual, movement-related and visuomotor neurons. The visual neurons respond to visual stimuli, with about half of them responding stronger to stimuli destined to be saccadic targets. Movement-related neurons fire before and during saccades. Visuo-motor neurons are a mixture of the former two types exhibiting both visual and movement-related activity. The FEF plays an important role in the active disengagement from current fixation before the start of a new saccadic eye movement. In addition, the FEF controls the triggering of intentional saccades and amplitude of both intentional and reflexive contralateral saccades.

The SEF in the rostral end of the supplementary motor area (SMA) projects to

the FEF, SC and brain stem saccade generator. The SEF is involved mainly in planning sequences of intentional saccades and coordinating planned saccades with other body movements. Similar to hand movement, the cortical control of saccades shows a contralateral organization. Electrical stimulation of the FEF (Godoy et al., 1990) or SEF (Lim et al., 1994) of one hemisphere elicits saccadic eye movements directed to the contralateral side of the activated hemisphere.

Saccadic eye movements can also be initiated by the lateral intraparietal area (LIP) also called parietal eye fields (PEF). In humans the PEF is presumably located in the intraparietal sulcus. This area can trigger saccades via projections to the FEF and SC but has no direct access the brainstem saccade generator. The PEF is believed to control disengagement of fixation upstream of the FEF as well as triggering of reflexive visually guided saccades. The PEF and FEF overlap in their role of controlling visually guided saccades. However, it appears that the PEF predominantly controls reflexive visually guided saccades whereas the FEF is more important for mediating intentional visually guided saccades.

In addition to the above brain structures that initiate saccades, there are other cortical areas more indirectly involved with saccade preparation. The posterior parietal cortex (PPC), adjacent to the PEF, is an important area concerned with the control of visuo-spatial attention. Since visual-spatial attention and eye movements are closely interrelated, the PPC also is involved with the control of eye movement. The PPC projects both to the PEF and PFC. Lesions of the PPC result in neglect of stimuli in the ipsilateral visual hemifield, impairment of saccades to remembered visual targets and increased reaction times and decreased targeting accuracy for saccades directed to stimuli in the neglected hemifield. Finally, the dorsolateral PFC anterior to the FEF is involved in the control of memory guided saccades. This area receives afferents from the PPC and projects to the FEF, SEF and SC. The PFC also may be concerned with the regulation of predictive saccades before expected target jumps. This control is exerted presumably via the FEF. Furthermore, the PFC has been mentioned as a control center mediating inhibition of undesired reflexive saccades, most probably through its connection with the SC.

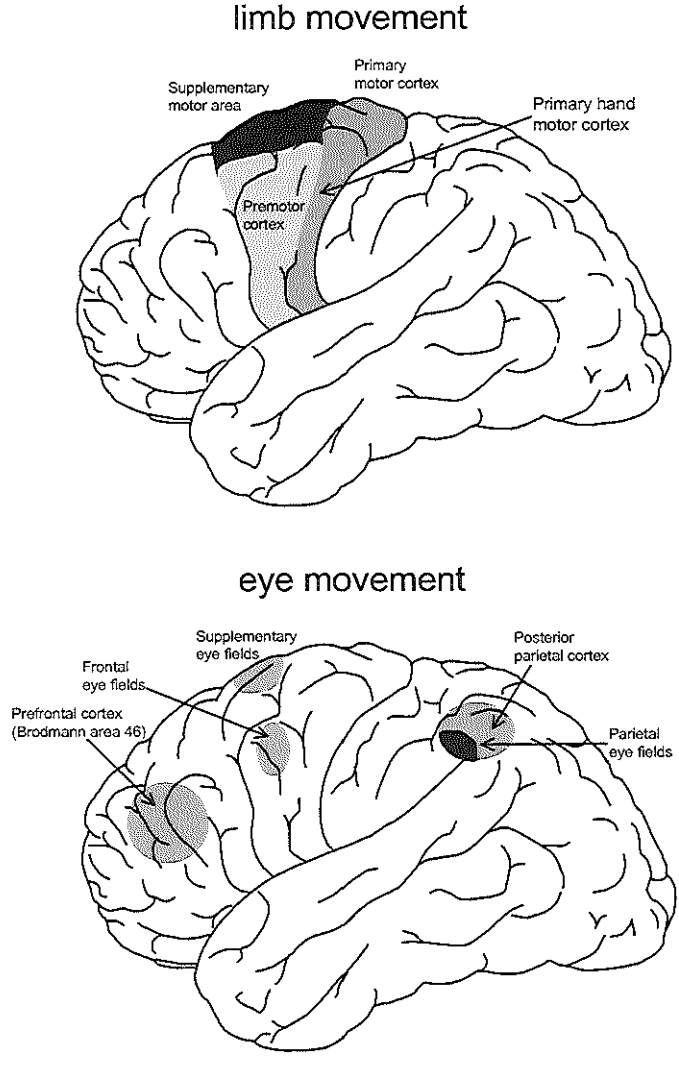


Figure 1: *Cortical areas controlling limb movement (top) and eye movement (bottom). (Adapted from E.R. Kandel, J.H. Schwartz and T.M. Jessell (Eds.), Principles of Neural Science, Fourth Edition. McGraw-Hill, 2000, p. 757 and Pierrot-Deseilligny et al., 1995.)*

1.2. Electro-encephalogram

In this thesis brain activity is examined by recording the electro-encephalogram (EEG). The EEG represents the electrical activity of the brain as recorded from metal electrodes placed on the scalp surface. The EEG technique allows for monitoring of brain activity from different locations at the same time and with high time resolution. The EEG signals mainly reflect the activity of neurons in the neocortex closest to the recording electrodes. Deeper brain structures like the hippocampus, thalamus and brain stem do not contribute significantly to the EEG. The recorded electrical potentials are generated predominantly by extracellular current flow induced by postsynaptic potentials in the apical dendrites of cortical neurons. Fig. 2 shows the structure of a neuron. It consists of a cell body (the soma), multiple dendrites and an axon. The dendrites are the antennas by which the neuron receives signals from other neurons. The neuron has a number of basal dendrites originating directly from the cell soma and one long apical dendrite with multiple branches. The neuron transmits electrical signals to other neurons by sending an action potential along its axon. An action potential is a short lasting disruption of the potential difference between in- and outside of the cell. The axon is also branched to contact dendrites of many other neurons. The point of contact between a neuron's axon and the dendrite of another neuron is called a synapse. The cell making the contact is named the presynaptic neuron and the receiving cell is termed postsynaptic neuron. When an action potential arrives at a synapse a chemical neurotransmitter is released in the synaptic cleft, a small gap between the presynaptic axon and postsynaptic dendrite. The neurotransmitter locally disturbs the resting potential across the postsynaptic cell membrane. The resting potential equals about -70 mV and is due to a net imbalance in concentration of mainly potassium (K^+), sodium (Na^+) and chloride (Cl^-) ions between the intra and extra cellular medium. The concentration gradient is maintained by an active mechanism; the sodium-potassium pump. Depending on the chemical compound of the neurotransmitter a synapse can either be excitatory or inhibitory. At an excitatory synapse the neurotransmitter causes the neuronal membrane to become highly permeable to sodium ions for 1 or 2 ms. During this time sodium ions migrate into the cell depolarizing (reducing) the negative membrane potential by 1 to 5 mV. At an inhibitory synapse the opposite happens through a 1-2 ms change in the permeability to potassium and chloride. Diffusion of these ions causes the membrane potential to be hyperpolarized (increased) by about 5 mV. The local changes in membrane potential are referred to as Excitatory Postsynaptic Potential (EPSP) and Inhibitory Postsynaptic Potential (IPSP), respectively. Many synapses (10^3-10^4) converge on the dendrites and soma of a single neuron and the currents generated by various postsynaptic potentials at any moment in time are summed. A neuron will transmit an action potential along its axon only when the graded changes of the resting potential caused by EPSPs exceed those due to IPSPs by a certain threshold. The current flow induced by an EPSP is illustrated in Fig. 3. A schematic drawing is shown of a neuron which receives an input from another neuron through a synapse at the distal end of its apical dendrite. When an action potential arrives at the synapse positive ions flow into the neuron creating an active current sink. The current induced by the ion inflow completes a loop by flowing back to the extracellular medium at other sites of the membrane creating a distributed

passive current source. The same basic principle applies for IPSPs, with a reversed direction of the current flow. A current source is created at the synapse and a current sink at other sites of the cell membrane.

The field potential generated by the extracellular currents of a single neuron is too weak to be measured at the cortical surface. For this, synaptic currents of many neurons need to be present at about the same time and these currents should have more or less the same direction. The extracellular currents generated by pyramidal neurons comply best with these qualifications. Pyramidal cells, most predominant in layers three and five of the cerebral cortex, have a single long apical dendrite crossing several cortical layers towards the brain surface. The apical dendrites of neighboring pyramidal neurons tend to be oriented parallel to each other and usually large populations of pyramidal neurons are simultaneously active. Therefore, the collective activity of extracellular currents from pyramidal neurons results in a potential field recordable at the brain's surface. Action potentials along the cell axons do not contribute significantly to the surface potentials. The action potential at any moment of time causes a depolarization across only a small area of the cell membrane. Because of this, the resultant electrical field attenuates much faster with distance than the field generated by an electronically conducted postsynaptic potential which extends over a much larger area of the membrane. Action potentials also have a very short duration (1-2 ms) and therefore tend to overlap much less than postsynaptic potentials.

Fig. 4 clarifies that the nature of synaptic events cannot be inferred directly from far field potentials recorded at the cortical surface. The illustration shows that an electrode located close to a current sink detects currents flowing away from the electrode into the cytoplasm as a negative potential while an electrode near the current source detects a positive potential. Therefore the electrical potential measured at a surface electrode will be negative for EPSPs at distal ends of the apical dendrites, in superficial cortical layers, and IPSPs near the cell soma's, in deeper layers. Conversely, EPSPs in deeper layers and IPSPs in superficial layers produce positive field potentials. In general, excitatory synapses are located further away fom the cell body than inhibitory synapses. The EEG is not measured directly from the brain's surface but from the scalp. Therefore, and because the cortex is folded, the EEG signals also depend on the orientation of the active patch of cortex with respect to the scalp electrodes. Finally, the EEG signals are attenuated and distorted by the intervening tissue and bone between the brain and the recording electrodes. As a result of volume conduction through the poorly conducting skull, activity in a small area of the cortex may result in widespread electrical field potentials across the scalp.

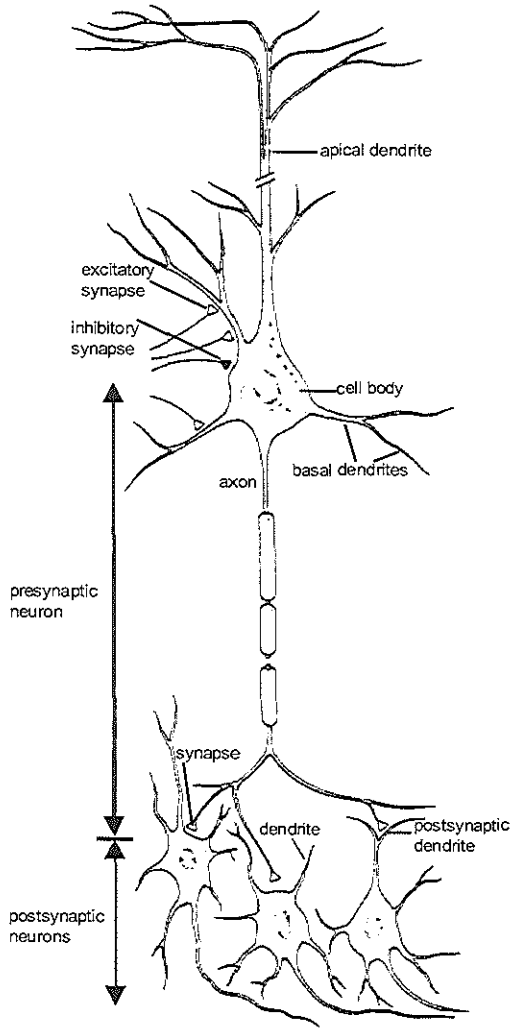


Figure 2: *Illustration of a nerve cell. (Modified from G. van Hoey, Detectie en bronlokalisatie van epileptische hersenactiviteit met behulp van EEG-signalen. Phd-thesis, University of Gent, Belgium, 2000, p. 7.)*

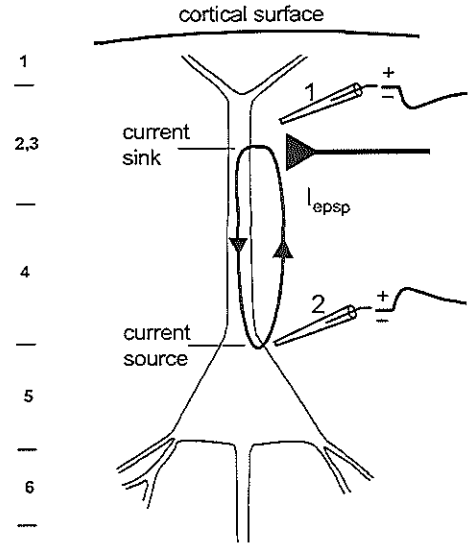


Figure 3: *Electrical current flow induced by an excitatory postsynaptic potential (EPSP) on the apical dendrite of a pyramidal neuron in the cerebral cortex. At the site of the EPSP, current flows across the cell membrane into the cytoplasm (current sink). The current (I_{epsp}) then descends through the dendritic cytoplasm and completes a loop by flowing back into the extracellular medium at the level of the cell's soma (current source). An extracellular electrode near the current sink (electrode #1) detects a negative potential; an electrode near the current source (electrode #2) records a positive potential. (Modified from E.R. Kandel, J.H. Schwartz and T.M. Jessell (Eds.). Principles of Neural Science, Fourth Edition. McGraw-Hill, 2000, p. 914.)*

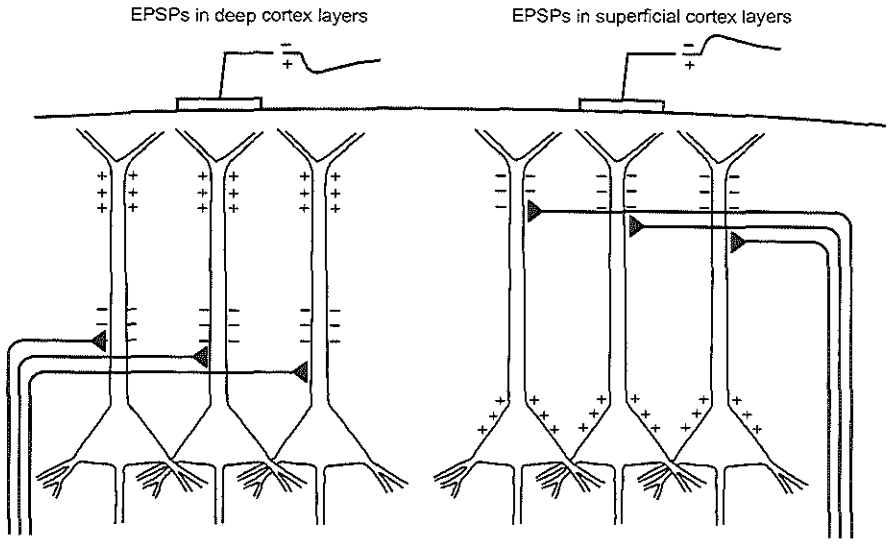


Figure 4: *The polarity of potentials recorded from the cortical surface depends on the location of the synaptic activity. EPSPs in deep layers (left) produce a positive potential at the cortical surface because the recording electrode is closer to the current source. Conversely, EPSPs in superficial layers (right) produce surface negativity because then the electrode is closer to the current sink. (Modified from E.R. Kandel, J.H. Schwartz and T.M. Jessell (Eds.), Principles of Neural Science, Fourth Edition. McGraw-Hill, 2000, p. 915.)*

1.3. Event related potentials

This thesis concentrates on cortical activities in the EEG evident as event related potentials (ERPs). These are brain potentials accompanying external or internal events such as the onset of a physical stimulus or the start of a motor response. When the brain activity is reproducible and time-locked to the event it can be made visible from the background EEG by constructing an averaged ERP response. This can be done in a laboratory setting by repeating the event several (typically > 100) times and recording the EEG during each event. Subsequently the recorded EEG epochs are synchronized on the event and averaged. In this way the signal to noise ratio of the event related potentials is improved because ongoing brain activity is suppressed while potentials time-locked to the event remain unaffected.

1.3.1. Readiness potential

Using the averaging technique, Kornhuber and Deecke (1965) observed brain potentials related to the initiation of voluntary hand movements in the scalp EEG.

Originally these investigators used the German term 'Bereitschafts Potential' (BP) to describe these premotor brain signals. Nowadays the English variant 'Readiness potential' is more common. The term is meant to indicate that the observed brain potentials reflect processing involved with preparation of a motor response. The premovement potentials consist of surface negativity which can be recorded over large parts of the skull and are presumably generated by EPSPs at the apical dendrites of pyramidal tract neurons (Arezzo and Vaughan, 1980). In a typical RP paradigm, subjects are asked to make a finger movement at self paced intervals of about 10-30 seconds. During execution of the task the EEG is recorded and the occurrence of finger movements is detected by recording electrical activity from the agonist muscle (ElectroMyoGram: EMG) and/or by using a response measuring device (e.g., a push button). A typical RP waveform is depicted in Fig. 5 (top trace). In the averaged EEG aligned on movement onset, the RP is evident as a widespread negative potential shift starting as early as 1.5 seconds preceding the finger movement. The RP is initially symmetrical over both cerebral hemispheres. At about 500 ms before movement onset the RP becomes asymmetrical. During this period cortical negativity starts to increase more strongly with preponderance over the hemisphere contralateral to the movement side. The asymmetrical part of the RP has also been referred to as the Negative Slope (NS': Shibasaki et al., 1980). Following the NS', at about 100 ms before movement onset, a small bilaterally symmetric premotion positivity (PMP) is commonly observed. After the PMP negativity resumes to reach a maximum during movement execution. This final negativity has been termed the motor potential (MP). Post-movement the RP is ended by one or more positive potentials.

The initial symmetrical part of the RP has been attributed to bilateral activation of premotor areas (Brunia et al., 1988) and/or the supplementary motor area (SMA: Deecke and Kornhuber, 1978; Ikeda et al., 1992; Ikeda et al., 1993; Lang et al., 1991). The subsequent lateralized parts NS' and MP are believed to originate from primary motor cortex (MI) activation with contralateral preponderance (Neshige et al., 1988; Arezzo and Vaughan, 1975). There is also evidence that MI is the sole generator of the RP, with symmetrical activation for the early part and activation largest over the contralateral hemisphere for the NS' and MP (Neshige et al., 1988; Bötzel et al., 1993; Roland et al., 1980; Walter et al., 1992, Böcker et al., 1994). A clear origin for the PMP has not been found and therefore its status as reflecting an independent cortical mechanism has been questioned. The PMP might be an epiphenomenon caused by relaxation of the NS' negativity before onset of the MP (Neshige et al., 1988; Böcker et al., 1994). In addition to potentials associated with movement preparation, cortical activity related to various other non-specific psychological processes such as attention, arousal and willingness to move may contribute to the recorded activity. The positive potentials following the RP are believed to reflect the closure of premovement cortical mechanisms as well as re-afferent brain potentials from primary somatosensory areas (SI).

A correlate of the RP preceding hand movement also has been reported preceding self-paced saccadic eye movements (Becker et al., 1972; Kurtzberg and Vaughan, 1982; Thickbroom and Mastaglia, 1990; Evdokimidis et al., 1991). The observed presaccadic negativity has been associated with activation of cortical ocular

motor areas like the frontal eye fields (Kurzberg and Vaughan, 1982; Klostermann et al., 1994) or supplementary eye fields (Moster and Goldberg, 1990).

1.3.2. Contingent negative variation

Slow negative brain potentials from the brain are also observed during the interstimulus interval in so-called two stimulus paradigms. In these paradigms an initial warning stimulus S_1 signals that after a given time a second imperative stimulus S_2 will occur. The cortical negativity in the S_1-S_2 interval was discovered by Grey Walter et al. (1964) and termed contingent negative variation (CNV) because the potential depends on the fact that the S_1 and S_2 stimuli are contingent on each other. S_1 serves as a warning stimulus but can also provide information about the required action after S_2. The imperative S_2 may signal the subject to execute (or withhold) a motor response. Alternatively a cognitive task may be required. For example when pictures from a collection of human faces are presented and the task for the subjects is to internally count the number of faces they have seen before. In later CNV studies the S_1-S_2 time interval has commonly varied between 1 and about 10 seconds. With long interstimulus intervals (> 2 s) two separate waves can be distinguished, the initial CNV (iCNV) and terminal CNV (tCNV). A representative CNV profile is shown by the bottom trace in Fig. 5. The iCNV is evident during the first 1-3 s following S_1. This component is largest over the frontal cortex and assumed to reflect cortical activity associated with processing of the warning stimulus, or possibly an orienting response. The tCNV during the remaining period between the end of the iCNV and the onset of S_2 is largest at the vertex. The tCNV is proposed to be a composite potential generated by a diversity of cortical sources. The waveform may reflect the activation of cortical motor areas involved with motor preparation as also present in the RP. Other contributing mechanisms may relate to non-motor functions such as working memory and effort necessary to complete the task. The tCNV is also believed to consist of a Stimulus Preceding Negativity (SPN: Damen and Brunia, 1987; Brunia and Damen, 1988) reflecting cortical mechanisms associated with anticipation of S_2. In general the tCNV is ended by a return to prestimulus baseline or by cortical positivity.

1.3.3. Lateralized readiness potential

As indicated, the RP and CNV are composite potentials reflecting processing concerned with movement preparation and various other non-motor functions. If an experiment is performed with left and right side movement, motor related contributions to the recorded ERPs can be extracted using the lateralized readiness potential (LRP). A detailed explanation of the LRP measure is provided in Fig. 6. In brief, the LRP is derived from the EEG by first subtracting for each experimental trial cortical activity recorded over the hemisphere ipsilateral to the movement side from activity over the hemisphere contralateral to the movement side and subsequently averaging the obtained difference potentials across trials with left- and right side movement (Coles et al., 1995). In the case of hand movements, earlier work has shown that inter-hemispheric lateralization in the LRP primarily indexes differential activation of precentral left and right hand motor cortices (Bötzel et al., 1993; Böcker et al., 1994; Praamstra et al., 1996).

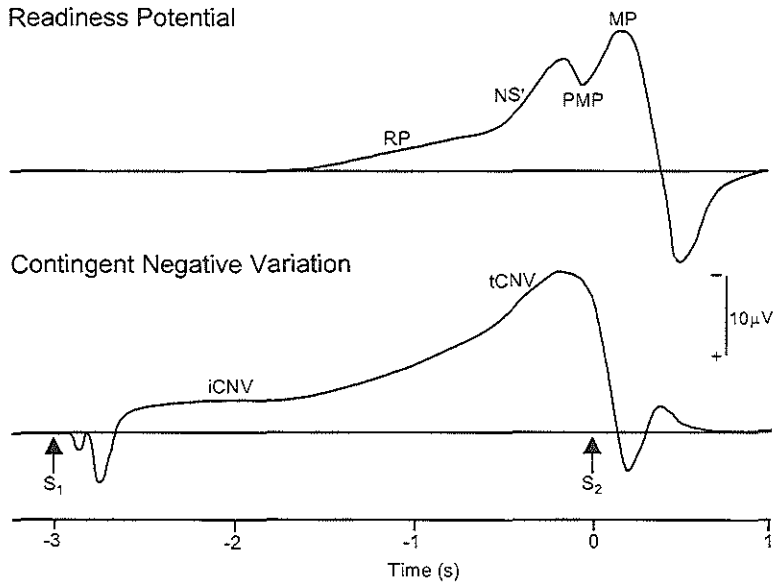


Figure 5: *Theoretical waveforms of the Readiness Potential (RP) measured before self-paced hand movement (top) and the Contingent Negative Variation (CNV) observed in a two stimulus reaction task (bottom; the interstimulus interval is 3 s). The RP is obtained after response synchronized averaging with movement onset at t = 0 s. The CNV is obtained after stimulus locked averaging with onsets of the warning stimulus S_1 and imperative signal S_2 at t = −3 s and t = 0 s, respectively (also indicated by vertical arrows).*

Several studies on cortical activity preceding saccadic eye movements also report a dominance of cortical response amplitude over the hemisphere contralateral to saccade direction (Thickbroom and Mastaglia, 1985; Moster and Goldberg, 1990; Klostermann et al., 1994). Related studies tentatively suggested that the asymmetry may indicate differential activation of cortical ocular motor areas such as the FEF or SEF. However, the observed inter-hemispheric asymmetries may also be of non-motor origin. First of all because in the experiments on presaccadic brain potentials the LRP measure was not used to exclude non-motor related lateralizations. Instead, inter-hemispheric asymmetries were assessed from the 'raw' difference potentials between corresponding electrodes over the left and right hemispheres. If both left- and rightward directed saccades are made, a correlate of the LRP for hand movement can also be computed for eye movement. This is done by subtracting cortical activity over the hemisphere ipsilateral to saccade direction from activity over the contralateral hemisphere for individual trials and then averaging the contra - ipsilateral differences. However, with eye movements the LRP may still contain non-motor related asymmetries. Earlier studies have reported that before a saccadic eye movement the focus of attention is

directed away from current fixation toward the saccade target (Posner, 1980; Fischer and Breitmeyer, 1987; Posner and Petersen, 1990; Duhamel et al., 1992). Covert attention shifts may result in non-motor specific ERP lateralization (Lang et al., 1984; Deecke et al., 1985; Harter et al., 1989; Yamaguchi et al., 1994; Yamaguchi et al., 1995, Wascher and Wauschkun, 1996). Since, depending on eye movement direction, attention is directed either to the right or left visual hemi-field, hemispheric cortical response dominance may switch for right- and leftward saccades and accompanying attention related asymmetries may influence the LRP difference waveforms.

1.3.4. LRP analysis of the flanker reaction task

The LRP indexes differential activation of left and right cortical motor areas that may or may not be sufficient to trigger an overt limb movement. As such, the LRP can also be used to measure covert tendencies for motor activation. The LRP has been particularly helpful in studies investigating temporal aspects of human information processing. An important result of this work concerns the LRP based analysis of cortical processing during performance of the flanker reaction task (Eriksen and Eriksen, 1974). In a flanker task, typically a target letter signaling a movement of the right or left hand (e.g., *S*: right hand; *H*: left hand) is presented in the middle of a letter string. The surrounding letters are either the same as the target (congruent flankers, e.g., *SSSSS* or *HHHHH*) or call for an opposite hand response (incongruent flankers, e.g., *HHSHH* or *SSHSS*). Reaction times in these tasks are consistently found to be increased after incongruent flankers. Eriksen and co-workers argued that this flanker effect may be caused by competition at the motor activation level. According to their continuous flow model, motor responses are activated as soon as stimulus information becomes available. If more flanker than target letters are displayed movement selection is initially based on the identity of the flankers. Later, when the central target letter is located, motor activation in agreement with the target becomes more important. Reaction times following incongruent stimulus displays can be delayed due to a conflict between flanker and target based motor responses. The concept of early incorrect motor activation after incongruent flankers has been supported by the finding of an initial positive deflection of the LRP waveform (Gratton et al., 1988; Kopp et al., 1996a, Kopp et al., 1996b; Praamstra et al., 1998). The LRP positivity indicates that during a short period before correct hand selection, the motor cortex mediating incorrect hand movement is activated stronger than the motor cortex controlling the correct hand (Gratton et al., 1988).

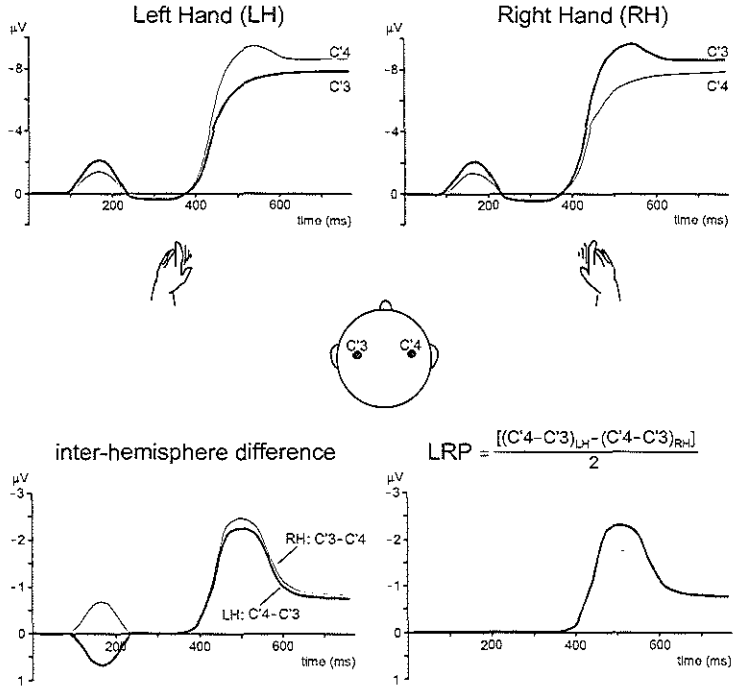


Figure 6: *Derivation of the LRP measure. The top panels show idealized cortical response profiles recorded over left and right primary motor cortices (electrodes C'3 and C'4) during a task where subjects are asked to respond as quickly as possible to a stimulus that signals a movement of either the left or right index finger. Brain potentials on trials with left hand movement are depicted on the left, potentials on trials with right hand movement are indicated on the right. In the ERPs, an initial negative enhancement with largest amplitude over the left hemisphere is evident between 100 and 250 ms after stimulus onset (t = 0 ms). The negative potential reflects brain activity related to processing of the stimulus. After about 400 ms, cortical activation associated with preparation and execution of the hand movement becomes evident. With left hand movement cortical response amplitudes are more negative over the right (C'4) than the left (C'3) hemisphere. For right hand movement the amplitude difference is reversed with largest negativity over the left hemisphere. These voltage differences reflect increased activation of the motor cortex contralateral to the movement side. In the bottom left panel the asymmetries are indicated as a right – left difference potential (C'4 – C'3) for left hand movement and a left – right difference potential (C'3 – C'4) for right hand movement. In the time window before 250 ms post stimulus onset, the difference potentials are still influenced by stimulus-evoked brain activity. In the bottom right panel the LRP profile is shown in which stimulus related asymmetries are removed by averaging the difference potentials across trials with right and left hand movement. (Modified from Praamstra et al., 1998.)*

1.4. Control of action

1.4.1. Motor inhibition

According to contemporary theories on executive control, the regulation of behavior is mediated through inhibition of planned actions (Logan and Cowan, 1984). Brain activity associated with motor response inhibition is commonly examined by comparing event related potentials following stimuli that command or prohibit a specific motor response. For this purpose, typically Go/NoGo reaction time paradigms have been used. In a Go/NoGo task a predefined motor response is required following Go stimuli while the response should be omitted following NoGo stimuli (Karlin et al., 1970). Several Go/NoGo studies report an ERP negativity usually labeled N2 which is larger on NoGo trials with proper movement suppression, compared with Go trials, with correct movement execution (Simson et al., 1977; Eimer, 1993; Jodo and Kayama, 1992; Jodo and Inoue, 1990; Kok, 1986; Pfefferbaum et al., 1985; Gemba and Sasaki, 1989; Naito and Matsumura, 1994a,b; Falkenstein et al., 1995; Naito and Matsumura, 1996). Component N2 is found maximal across frontal brain areas and peaks at about 200-300 ms after the onset of the NoGo stimulus. The Go/NoGo effect on the N2 component has been related to cortical processing associated with motor inhibition (Pfefferbaum et al., 1985; Kok, 1986; Eimer, 1993).

The N2 is commonly found to be much smaller after auditory than after visual NoGo stimuli (Falkenstein et al., 1995; Falkenstein et al., 1999). Falkenstein et al. (1999) accordingly proposed that the N2 may originate from modality specific generators in the brain, with the field potentials from the source after auditory stimuli projecting less well to the scalp EEG electrodes. This assumption is also supported by a study of Gemba and Sasaki (1990) who found different locations of an inhibition related electrical potential in monkeys after visual and auditory NoGo stimuli. The NoGo potential after visual stimuli was observed primarily in caudal regions of the dorsal bank of the principal sulcus. The potential after auditory stimuli appeared more in rostral regions of this formation. The finding that the N2 differs across stimulus modalities implies that the inhibition mechanism presumed to underly the N2 exerts its influence on premotor processing levels rather than on the final motor output stage. This concept agrees with a study Pfefferbaum et al. (1985) who found an N2 component also after inhibition of non-motor tasks.

In addition to the N2 Go/NoGo effect, several Go/NoGo studies report an enhancement in amplitude of the late positivity P300 on NoGo trials compared with Go trials (Karlin et al., 1970; Hillyard et al., 1976; Simson et al., 1977; Pfefferbaum et al., 1985; Pfefferbaum and Ford., 1988; Kok, 1986; Jodo and Inou, 1990; Roberts et al., 1994). In addition, several of these studies found that the P300 on Go and NoGo trials exhibit a different scalp distribution. The P300 after Go stimuli is largest at parietal sites whereas the P300 after NoGo stimuli is most pronounced at frontal-central scalp sites (e.g., Karlin et al., 1970; Hillyard et al., 1976; Simson et al., 1977; Pfefferbaum et al., 1985; Pfefferbaum and Ford., 1988; Roberts et al., 1994). The P300 component also is generally found to be delayed on NoGo trials (e.g., Simson et al., 1977; Pfefferbaum et al., 1985; Pfefferbaum and Ford., 1988; Roberts et al., 1994). As for the N2 Go/NoGo effect, the P300 Go/NoGo effect has been related to inhibition of task-inappropriate movements (Karlin et al., 1970; Roberts et al., 1994). However, this theory is

confronted with two main difficulties. The first is a methodological problem related to the fact that the P300 Go/NoGo difference may be influenced by differential overlap of movement-related negativity. The frontocentral P300 in NoGo trials is generally observed at about the time when motor activation occurs on Go trials. Movement production on Go trials is believed to be accompanied by a negative motor potential (MP) in the ERPs. Because the MP is absent on NoGo trials, the ERPs on NoGo trials are likely to be less negative than the ERPs on Go trials shortly before and during the motor response. This could in fact explain the observed P300 Go/NoGo effect. A possible contribution of movement related brain activity to the Go/NoGo difference has been confirmed in a simulation study by Kok (1988). An influence of motor potentials also was suggested by the findings of Kopp et al. (1996b). These investigators added NoGo target stimuli in a flanker reaction task and compared ERPs after NoGo stimuli that were either surrounded by flankers identical to the imperative Go stimuli (specific response priming) or by neutral flankers with no response information. In this way motor-related Go/NoGo differences could be excluded. In the ERPs, the N2 component was larger after NoGo stimulus with specific priming (requiring inhibition) than after neutral NoGo displays. In contrast, a frontocentral P300 enhancement compared with neutral NoGo stimuli was absent. The finding by Pfefferbaum et al. (1985) of a more anterior scalp distribution of the NoGo P300 compared with the Go P300 in a cognitive task suggests however that the P300 Go/NoGo effect cannot be entirely due to differential overlap of negative motor potentials.

The second more important problem with the inhibition proposal for the P300 concerns the finding of several studies that the P300 enhancement after NoGo stimuli occurred long after the time at which overt movements were made after Go stimuli (e.g., Eimer 1993). Thus the NoGo P300 seems to be too late for an inhibition related potential. In sum, considering both overlap of movement related cortical negativity and the long latency of the P300, the hypothesis relating the P300 Go/NoGo effect to motor inhibition remains questionable.

1.4.2. Error monitoring

A negative ERP component also has been identified that appears specifically when movement errors are made. This component was labeled the 'error-related negativity' (ERN: Gehring et al., 1993) or 'error negativity' (N_e: Falkenstein et al., 1991). In this thesis the term N_e is used. A review on the N_e component is provided in a paper by Falkenstein et al. (2000). The N_e is evident as a sharp negative deflection in the ERPs with frontocentral distribution, peaking about 80 ms after an error response. Several hypotheses have been proposed with regard to the functional significance of the N_e. First, since movement errors are usually replaced by a correct motor response the N_e may be a correlate of an error correction mechanism. However, in choice reaction tasks the N_e has been observed with similar amplitude on trials with corrected and uncorrected errors (Falkenstein et al., 1996). Furthermore, in Go/NoGo tasks the N_e is also present on NoGo trials in which a motor response is accidentally executed (Falkenstein et al., 1994; Falkenstein et al., 1995). An N_e like component has also been found after failures to reach a response deadline (Luu et al., 2000). Because an N_e accompanied these errors which cannot be undone it seems unlikely that the N_e is

involved in immediate error correction. Alternatively, the N_e may represent an error compensation mechanism that acts to prevent errors from recurring on future trials. Some evidence for this comes from Go/NoGo reaction studies by Gehring et al. (1993) and Scheffers et al. (1996). These investigators found a weak association between amplitude of the N_e and error compensation; reaction times on correct Go trials tended to be delayed if preceded by NoGo error trials in which a large N_e component was evident in the ERPs.

The evidence obtained about the N_e thus far is most consistent with a concept relating the negativity to an error monitoring system that acts to detect a mismatch between representations of the motor response that should be made and the response which is actually activated (Falkenstein et al., 1991; Gehring et al., 1993; Falkenstein et al., 1995; Scheffers et al., 1996). This hypothesis is supported by several studies which found that the occurrence of the N_e is positively related to the detectability of an error (e.g., Falkenstein et al., 1996; Bernstein et al., 1995). The N_e becomes larger and/or starts earlier when the degree of error, i.e., the difference between representations of the required and actual response, is larger. Additional evidence comes from experiments showing that the N_e is less pronounced when the representation of the task-appropriate response is degraded. For example, Falkenstein et al. (2000) found the N_e to be larger in conditions where response accuracy was emphasized than in conditions where response speed was emphasized. This finding was explained by assuming that determination of the correct response is conducted less thoroughly under high time pressure, compromising the error detection process. In recent experiments a small N_e like negativity has also been observed after correct motor responses (Falkenstein et al., 2000; Vidal et al., 2000). Related studies noted that a comparison between representations of the actual and required motor response is also necessary on correct trials. Therefore, it was proposed that the N_e may represent the response checking process itself rather than the outcome of this process (the detection of an error).

The error detection or response checking mechanism underlying the N_e can act on information on the correct response available after stimulus-response mapping has finished. The error system may obtain this information from the lateral prefrontal cortex (Gehring and Knight, 2000). Since the N_e deflection begins as early as the first muscle activity (EMG) mediating the incorrect response (Gehring et al., 1993), the system probably uses a representation of the actual response obtained from central sources. This could be for example an efference copy of the command issued by the primary motor cortex controlling the movement.

If an error is detected an attempt will likely be made to inhibit the error. Therefore, instead of response checking, the N_e may reflect an error inhibition mechanism. Specifically, the N_e could be similar to the N2 component described in the previous paragraph (Kopp et al., 1996a, 1996b). However, Falkenstein et al. (1999) found in a Go/NoGo task that the N2 varied with stimulus modality (visual/auditory: see previous paragraph) and task performance (high/low error rates) whereas the N_e did not. Furthermore, Falkenstein and colleagues (1999) found that the N_e exhibited a more central scalp topography than the N2. From these results Falkenstein et al. (1999) concluded that the N2 and N_e reflect different cortical mechanisms. Additional, though indirect, evidence against an error suppression hypothesis for the N_e comes from the earlier mentioned finding that N_e amplitude is positively correlated with the degree of

error. If N_e amplitude reflects the strength of inhibitory activation an inverse relationship between the N_e and error size would rather be expected, i.e., small response errors should be accompanied by a large N_e (strong inhibition) and vice versa.

1.5. Research questions

Chapters 2 and 3 of this thesis concentrate on scalp recorded brain potentials accompanying hand and saccadic eye movement. In chapter 2 the question is addressed whether inter-hemispheric asymmetries of motor function as observed preceding hand movements are also present before saccadic eye movements. To study motor related asymmetries, the LRP measure was computed for both movement modalities. In addition, to avoid contamination of the LRP by asymmetries due to covert attention shifts, movements were made in the context of a CNV paradigm. In a CNV task, attention during the interval between onsets of the warning stimulus S_1 and imperative stimulus S_2 is focused mainly on the position where S_2 will be presented such that premovement shifts of attention are suppressed. Lateralizations of non-motor origin also were examined. To this end, the CNV stimuli were presented in the left visual hemifield. Half-field visual stimulation likely induces an asymmetry in primary sensory processing, because the left visual hemifield projects directly to the right visual cortex. In addition, because visuospatial attention is to be allocated to left visual field, according to Lang et al. (1984) and Deecke et al. (1985) a preponderance of cortical activity over parietal areas of the right cerebral hemisphere was expected. A new measure complementary to the LRP will be introduced to evaluate non-motor related lateralizations of the recorded ERPs.

The imperative stimulus S_2 in the CNV task of chapter 2 was a Go/NoGo stimulus. In chapter 3, data from the same experiment was used but now with primary focus on the ERPs recorded following S_2. Specifically, the N2 and P300 components on correct trials and the N_e on error trials. In earlier studies ERP correlates of response inhibition and action monitoring have been studied primarily for hand movement (e.g., Jodo and Inoue, 1990; Roberts et al., 1994; Falkenstein et al., 1995; Falkenstein et al., 1995). In chapter 3, ERPs following Go and NoGo stimuli accompanying either hand or saccadic eye movement were compared to examine whether the Go/NoGo effects on ERP components reported in earlier studies are characteristic for hand movement or whether comparable effects are found across movement modalities.

In chapter 4 ERPs, lateralized readiness potentials (LRPs) and reaction performance were examined in a flanker reaction task. This task was performed only with hand movement as effector. As mentioned in paragraph 1.3.4, reaction times in flanker tasks are generally increased after incongruent flankers. The reaction delay has been attributed to a conflict between flanker and target based motor responses. However, in addition to differences in motor related processing, flanker induced differences in perceptual evaluation may also contribute to the flanker effect on reaction times (Eriksen and Schultz, 1979; Hoffman, 1979; Duncan and Humphreys, 1989; Smid et al., 1991). Motor response latencies may be delayed after incongruent flankers because recognition of the central target takes longer when flankers and target are dissimilar. In a standard flanker task the influence of the flankers on motor and perceptual processing has similar effects on task performance, both induce slowed

reaction times on incongruent flanker trials. In the study of chapter 4 the standard flanker task was modified to examine whether the origin of the flanker effect on task performance is predominantly located at the motor activation or at the perceptual level.

An additional goal of this study was to further examine the question whether ERP components N2 and N_e relate to the same underlying cortical mechanism or represent functionally distinct mechanisms. In the ERP waveforms recorded during performance of flanker tasks, typically a frontal negative component is observed especially following incongruent flankers (Kopp et al., 1996a; Kopp et al., 1996b). Since there is a tendency for activating the incorrect hand after incongruent flankers, as also indicated by the LRP, the negativity presumably corresponds to the N2 component associated with motor inhibition (paragraph 1.4.1). Furthermore, on trials with movement errors a negative component is found which presumably corresponds to the N_e error negativity (paragraph 1.4.2). Falkenstein et al. (1999) correctly indicated that if their hypothesis that the N2 and N_e are functionally distinct were true then an N2 should also be present on error trials before the N_e. However, in the Go/NoGo task employed by these investigators clear evidence for an N2 preceding an N_e on error trials was not found. Falkenstein and co-workers (1999) explained this negative finding by noting that the N_e on error trials occurs only slightly later than the N2 on correct trials. Therefore, an N2 on error trials could be covered by the leading flank of the N_e. Previous work has shown that N_e is time-locked more closely to the motor response than to the stimulus, peaking shortly (in general earlier than 150 ms) after the start of incorrect peripheral motor activation (Falkenstein et al., 1991; Falkenstein et al., 1999; Leuthold and Sommer, 1999). Therefore, the N_e component likely appears at the same latency as the N2 since errors usually are early premature motor activations evident at about or just before the time at which the N2 is observed. In the study of chapter 4 a multi-attribute target stimulus was introduced so that incorrect hand movement could be induced not only by the flankers but also by partial information about the target stimulus. The target based movement errors occur later than flanker triggered errors and consequently the N_e is also expected to be delayed in the ERPs for trials with these late movement errors. Hence, overlap of a possible N2 by the N_e component is reduced and an N2 preceding an N_e on error trials should be more conspicuous. That is, when the N2 and N_e really do represent different cortical mechanisms.

2

Inter-hemispheric lateralization of event related potentials; motor versus non-motor related cortical activity

Abstract

To study hemispheric lateralization of cortical potentials associated with motor and non-motor function, cortical activity was recorded accompanying either finger extension or saccadic eye movements in a contingent negative variation (CNV) paradigm.

Subjects viewed computer generated pacing stimuli, presented in the left visual hemi-field, and were instructed to either initiate or inhibit a motor response following an imperative signal. Motor related lateralization was assessed by means of the lateralized readiness potential (LRP). In addition, a measure complementary to the LRP was introduced to investigate Non-Motor related Lateralization (NML).

Contralateral inter-hemispheric lateralization was evident in the LRP preceding finger movement but was absent prior to eye movements. However, pre-saccadic cortical response profiles did exhibit a right hemispheric, non-motor related lateralization (NML) during stimulus presentation. Comparable non-motor specific lateralization was found for finger extension.

Results of the present study suggest that non-motor related lateralization may be a contributing factor to the frequently reported inter-hemispheric asymmetry preceding self-initiated saccadic eye movements. Results of the present study also suggest that the latter may be related to a covert shift of visuospatial attention toward the saccadic target. Associated shifts of attention are suppressed in a CNV paradigm where attentional focus is primarily on the CNV stimulus during the pre-saccade period.

2.1. Introduction

In studies on scalp recorded cortical activity related to stimulus expectancy and motor preparation, investigations of inter-hemispheric amplitude asymmetries in the evoked cortical response profiles facilitate the distinction between motor versus non-motor related cortical processing (e.g., De Jong et al., 1988; Gratton et al., 1988; Hackley and Miller, 1995; Wascher and Wauschkun, 1996). Reported as reflecting motor related cortical processing, hemispheric response asymmetries have been identified in the readiness potential (RP) (Deecke et al., 1969) preceding voluntary limb movements (e.g., Sommer et al., 1994). Several investigations suggest that motor related lateralization mainly represents activation within the pre-central motor cortex involved in execution of the required motor response (Bötzel et al., 1993; Böcker et al., 1994; Praamstra et al., 1996). A contribution of the supplementary motor area (SMA) involved in both early as well as late stages of planning and preparation of self-initiated movements, also has been suggested (Ikeda et al., 1992).

A correlate of the RP accompanying limb movement also has been recorded preceding self-initiated saccadic eye movements (Becker et al., 1972; Kurtzberg and Vaughan, 1982; Thickbroom and Mastaglia, 1990; Evdokimidis et al., 1991). Several studies on pre-saccadic cortical activity report a dominance of cortical response amplitude over the hemisphere contralateral to saccade direction (Thickbroom and Mastaglia, 1985; Moster and Goldberg, 1990; Klostermann et al., 1994). Related studies suggest that response lateralization may be due to activation of cortical ocular motor areas such as the frontal eye fields (FEF) (Moster and Goldberg, 1990; Klostermann et al., 1994). However, non-motor specific cortical asymmetries also may contribute to the observed asymmetries. Non-motor related lateralization of event related potentials (ERPs) has been reported due to cognitive processes such as covertly directed attention (Lang et al., 1984; Deecke et al., 1985; Harter et al., 1989; Yamaguchi et al., 1994; Yamaguchi et al., 1995, Wascher and Wauschkun, 1996). For example, Klostermann and colleagues (1994) have suggested that besides activation of the FEF, left-hemispheric lateralization of cortical activity preceding rightward saccades, particularly over parietal areas, may also reflect directed attention toward the right visual hemi-field. Previous experimental findings purport that saccadic eye movements are preceded by a shift of visuospatial attention (Posner, 1980; Fischer and Breitmeyer, 1987; Posner and Petersen, 1990; Duhamel et al., 1992) and, as demonstrated by Lang et al. (1984) and Deecke et al. (1985), lateralization associated with directed attention markedly modifies hemispheric lateralization of the readiness potential.

The confounding effects of covert attentional shifts may be avoided by employing a contingent negative variation (CNV) paradigm. In a CNV test protocol, attention is focussed mainly on the CNV stimuli and as such, pre-saccadic shifts of attention are suppressed. Recently, Wauschkun et al. (1997) employed a CNV paradigm with saccadic eye movement. However, inter-hemispheric asymmetry of cortical activity preceding eye movements was not found. Evdokimidis et al. (1992) also investigated lateralization of cortical negativity preceding saccades in a CNV-like paradigm. In the study of Evdokimidis et al., pre-saccadic lateralization was detected, although only for self-initiated saccades towards predesignated target locations.

In the present study, a CNV test paradigm was employed to investigate and

compare both motor and non-motor related hemispheric lateralization of cortical activity recorded during saccadic eye movement as well as during finger movement.

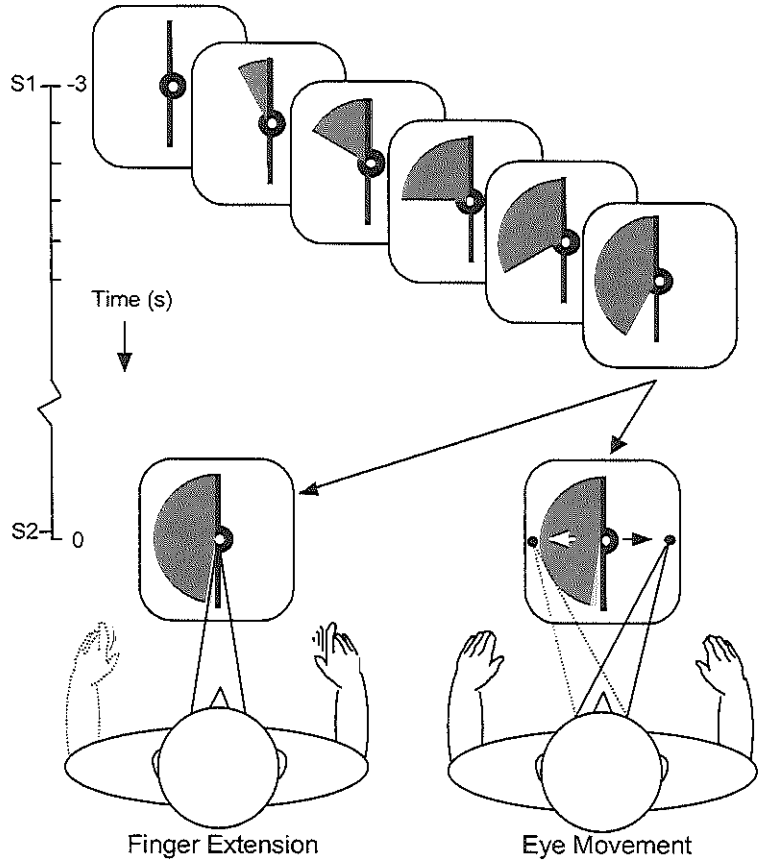


Figure 1: *Go/NoGo experimental paradigm with left half-field stimulation. The visual stimulus consists of a cartoon animation of a half-circle sketch. Subjects are instructed to maintain central fixation during the computer animation. The computer animation is completed in three seconds. In the illustration, onset (labeled S1) and offset of the animation are at −3 s and 0 s, respectively. A change in circle fill color at 100 ms preceding completion of the half-circle sketch (labeled S2) signals whether a response is to be executed or withheld. For the finger extension tasks, a full extension of either the right (sketched in continuous lines) or left (dotted lines) index finger is required, while for the eye movement tasks, the subject switches from central fixation either to a marker positioned right (direction of gaze drawn in continuous lines) or left (direction of gaze drawn in dotted lines) of the CNV stimulus as illustrated. Screen background is depicted as white for illustrative purpose; the actual stimulus background was nearly black, saccadic targets were white.*

2.2. Methods and Materials

2.2.1. Subjects

Ten healthy subjects, consenting members of the department staff, participated in the study (7 males, 3 females; mean age 31.3 yrs, range 22-51). All subjects were right-handed, as assessed by means of the Edinburgh inventory (Oldfield, 1971), and had normal or corrected to normal vision. Further, test protocols and ethics committee approval were in accordance with the Erasmus University Medical Faculty as well as the tenets of the Declaration of Helsinki.

2.2.2. Stimulus and Procedure

Subjects sat comfortably in a reclining chair in a dimly lit room with arms supported by arm rests, hands positioned palm down, and head supported by a head-holder. A computer screen, displaying a pacing stimulus was positioned 81 cm in front of the subjects (Fig. 1). In the centre of the screen, a fixation point (radius 0.15°), which also was the centre of an imaginary circle, was presented. In each trial, the left half of the circle (radius 4.5°) was drawn during a computer generated cartoon animation. The half-circle sketch was completed in exactly three seconds. At 100 ms prior to stimulus completion, the circle fill color changed from grey to green or red, either color occurring with 50% probability. Subjects were instructed to initiate a motor response as quickly as possible when the stimulus color turned green and to withhold the response when the stimulus color turned red. Feedback on reaction time performance was provided at two and a half seconds following completion of the half-circle sketch by displaying a filled circle (radius 2°) at the centre of the computer screen. The circle color was green when response latency occurred within 200 ms, otherwise the circle color was red. The inter-trial interval was randomized between four and ten seconds. Subjects were instructed to maintain central fixation and to avoid eye blinks during the computer animation. To ensure proper compliance of the experimental test conditions as well as accurate identification of motor response onset, subjects as well as visual stimuli were constantly and directly monitored by the experimenter. In addition, eye and finger movement data were readily available by on-line computer aided monitoring of EOG and EMG activity. Furthermore, with finger movement, subjects were instructed to completely relax the operating hand positioned upon the arm rest such that muscle activity preceding the required motor action was negligible.

The test paradigm consisted of four response conditions conducted in separate sessions, including right finger extension, left finger extension, rightward saccadic eye movement and leftward saccadic eye movement (Fig. 1). In the eye movement paradigms, two white colored circles (radius 0.3°) displayed permanently along the horizontal meridian at 8.5° left and right from central fixation, superimposed on the dark background of the computer screen, served as saccadic targets. Following a required finger or eye movement, subjects were instructed to keep the active finger in extension or to maintain fixation of the saccadic target for about two seconds before returning to the initial position. The duration of each session was 21 min, separated into 7 blocks of 3 minutes each. The order of the four experimental sessions was counter-balanced across subjects. Prior to the experiment each subject completed a 15 minute

training session to become acquainted with the experimental task requirements. Five subjects also participated in a control study, implemented to investigate the extent to which the recorded ERPs reflect cortical activity associated with performing a Go/NoGo task. The control study was carried out in two sessions, a 'Go/NoGo' session with a rightward saccade as required response and a 'View Only' session. In the 'View Only' control session, subjects viewed the stimulus without additional task requirements. The stimulus configuration of the counter-balanced control study was similar to that used in the main experiments, except that the color change to green or red could occur at either 500 ms or 300 ms prior to stimulus completion. Session order also was counter-balanced across subjects.

2.2.3. Recording

Cortical activity was recorded with Ag/AgCl electrodes at twelve scalp loci. Scalp sites Cz and Pz were selected according to the standard International 10-20 system (Jasper, 1958). Sites C'3, C'4, and C"3, C"4 were positioned 1 cm anterior and 2 cm posterior to C3, C4, respectively (see e.g., Grünewald-Zuberbier et al., 1981). Electrodes F'3 and F'4 were placed 1 cm lateral and 2 cm anterior from C'3, C'4 over cortical areas where, in recent PET studies, the frontal eye fields have been located (Sweeney et al., 1996). To facilitate recording ERPs from the supplementary motor area, site FCz was positioned anterior to Cz at 10% of the nasion to inion distance (see e.g., Lang et al., 1984; Naito and Matsumura, 1994). Finally, to optimize the recording of primary visual activity, sites O'z, O'1 and O'2 were positioned across the occiput, 1 cm above the inion, on the midline and 5 cm left and right of the midline, respectively (Harding et al., 1996). All electrodes were referenced to linked earlobe electrodes. Electrode impedance was less than 5 kΩ. Although the electrode montage was selected to record ERPs from cortical areas as indicated, a direct correspondence between electrode position and underlying brain structures is limited, due to head volume conductor effects, tangential orientation of dipoles generating the ERPs and inter-subject variability regarding the location of brain structures relative to the scalp surface (e.g., Le and Gevins, 1993). Electro-encephalographic activity was amplified with a time constant of 5 seconds (0.032 Hz) and a high cut-off frequency of 100 Hz. Electro-myographic activity (EMG) was recorded, in bipolar derivation, with electrodes positioned over the left and right forearms covering the index finger extensor muscles (m. extensor indicis). Electro-oculography (EOG) was recorded from electrodes positioned at the outer canthi of both eyes. In addition, to monitor the occurrence of eye blinks and vertical eye movements, an additional electrode was positioned above the nasion and linked to the electrode positioned at the outer canthus of the right eye. EOG activity was amplified using a band-pass of 0.032 - 100 Hz; EMG recordings were high-pass filtered at 5.2 Hz. All electrophysiological activity was digitized at a rate of 256 Hz with 12 bit precision. Electrophysiological responses are depicted (see figures 2 - 8) negativity upwards.

2.2.4. Data analysis

In the present study, one of the primary interests concerned inter-hemispheric amplitude asymmetries of cortical activity related to execution of overt movements.

Therefore, except for the control studies, analysis was restricted to cortical response profiles recorded in the 'Go' condition. For the control experiments, as a relatively small number of trials was obtained, analysis included cortical activity recorded in both 'Go' and 'NoGo' conditions. From the electrophysiological data recorded in each trial, stimulus and response aligned epochs were constructed. Epochs subtended from 3.25 seconds *before* to one second *after* stimulus completion or movement onset. EOG onset, in the eye movement paradigms, and EMG onset, in the finger extension paradigms, were determined off-line (Barrett et al., 1985). EMG and/or horizontal EOG data were displayed on a computer monitor on which the onsets of response related activity were marked by positioning a vertical hairline cursor. In the stimulus aligned epochs, the first 250 ms of each epoch were used as pre-stimulus baseline. For response synchronized averaging, the initial 250 ms typically also contained the onset of the CNV stimulus. Accordingly for the latter, the baseline was computed over a shorter interval including the first 70 ms of each epoch. Epochs were visually monitored and controlled for artefacts. Trials containing eye movement artefacts, amplifier clipping, extensive EMG activity or electrophysiological drift were excluded from further analysis. Artefacts in the ERPs as a result of the required saccades in the eye movement conditions were corrected. Averaged horizontal EOG traces were fit to the averaged cortical response profiles by means of first-order linear regression. Subsequently, EOG traces multiplied by the calculated transmission coefficients were subtracted from the averaged cortical activity. On average, 60 trials per subject were obtained in each of the four response conditions of which about 20% were rejected due to recording artefacts.

2.2.4.1. Motor response latency

For finger extension, motor response latency was defined as the time interval between stimulus color change and onset of response related EMG activity. For eye movements, response latency was defined as the time interval between stimulus color change and saccade onset. Statistical analysis was performed by means of repeated measures analysis of variance (ANOVA) with within-subject variables, Movement Modality (finger extension vs. eye movement) and Movement Side (right vs. left finger extension, rightward vs. leftward eye movement).

2.2.4.2. ERP amplitude

Average cortical response profiles were constructed for each subject and response condition. Trials were included with motor response latency within one standard deviation of mean motor response latency. Mean motor response latency was obtained by averaging motor response latencies across subjects as well as across left and right finger extension or across right- and leftward saccades. Amplitude values of components identified in the averaged cortical response profiles were evaluated by means of repeated measures ANOVA with within-subject variables, Movement Modality, Movement Side and Electrode. For the control sessions, amplitudes of ERP components were evaluated with; Control Session ('Go/NoGo' vs. 'View Only') and Electrode as within-subject variables. Bonferroni's correction procedure was implemented to compensate for multiple comparisons in the statistical analyses. When within-subjects variables included two or more degrees of freedom, degrees of freedom

were adjusted following Geisser and Greenhouse (1958). However, to facilitate interpretation, statistical summaries of data analyses in the present study are described with uncorrected degrees of freedom.

2.2.4.3. Lateralized Readiness Potential (LRP) versus Non-Motor related Lateralization (NML)

Motor related inter-hemispheric amplitude lateralization was assessed by means of a lateralized readiness potential (LRP) measure (for more detail see De Jong et al., 1988; Gratton et al., 1988). Inter-hemispheric asymmetry computation for the LRP was $[(L-R)_{right\ response} + (R-L)_{left\ response}]/2$, with L and R homologous electrodes over the left and right hemispheres, respectively. The LRP is based on the fact that motor related lateralization for a right side response has an opposite sign compared with motor related lateralization for a left side response. The latter implies that motor related lateralizations evident in the LRP are effectively subtracted when the left-right inter-hemispheric asymmetry is averaged across right and left response conditions. As a result, the latter asymmetry computation, formulated as $[(L-R)_{right\ response} + (L-R)_{left\ response}]/2$, will represent primarily non-motor specific lateralization. That is, provided that motor related lateralization is comparable for either a right or left motor response. The asymmetry measure is accordingly termed Non-Motor related Lateralization (NML) in the present study. Note also that, for the present calculations: $(L-R)_{right\ response} = NML + LRP$ and $(L-R)_{left\ response} = NML - LRP$. Thus, the NML measure represents the mean inter-hemispheric asymmetry across right and left movement conditions, while the lateralized readiness potential (LRP) represents the standard deviation of the average asymmetry (that is, when the standard deviation is calculated with population parameter N instead of N-1). It is assumed that the NML represents overall lateralization as introduced by the experimental protocol, while the LRP reflects variance on overall lateralization due to the fact that the protocol is implemented with either right or left side movement as required action. As the NML measure is employed to extract non-motor (stimulus) related lateralization, it was derived from stimulus synchronized averaged cortical activity. The LRP measure was obtained from response synchronized instead of stimulus synchronized cortical activity, since amplitudes of motor related lateralizations are reported to be larger for LRPs derived using the former approach (Sommer et al., 1994).

For the LRP profiles, regression analysis was performed to identify a change in motor related lateralization within a time window covering the final second prior to movement onset. For a given data sample within this main time window, the window was divided into two contiguous sub-windows. The first sub-window extended from the beginning of the main window (t = -1 s) to the data sample; the second sub-window extended from the data sample to the end of the main window (t = 0 s: movement onset). A linear regression line was fit to the LRP profile in each sub-window. The latter procedure was repeated for each sample within the main time window, with the restriction that each regression function was fit to at least 51 data samples (199 ms). The sample was then selected for which first-order regression functions could be constructed that fit optimally to the LRP in each sub-window. Goodness of fit was assessed by

calculating the residual sum of squares for both resultant regression functions. Subsequently, an F-test was applied to examine if the regression functions fitted to the LRP profiles in the sub-windows preceding and following the selected data sample were significant. A build up of inter-hemispheric lateralization following the data sample was assumed when the slopes of both regression functions were significantly different, assessed by analysis of covariance, and when in addition, the slope of the regression line fitted to the LRP profile in the sub-window following the data sample was significantly different from zero, assessed by t-test. To account for multiple comparisons in the statistical analyses, significance level was set at $p = 0.01$ for each individual test.

Careful inspection of the NML profiles as outlined indicated four phases in the development of hemispheric asymmetry. Initially, transition latencies between subsequent phases were determined by visual inspection. Next, three 500 ms time windows (selected to prevent overlap of adjacent windows) were defined and centred on the resultant transitions. Subsequently, a linear regression method, similar to the analysis used for examining the LRP, was employed to objectively identify the transition latencies. Following computerized identification, an analysis window was defined, subtending from 2500 ms prior to stimulus offset, $t = -2500$ ms, to stimulus offset, $t = 0$ ms. The first 500 ms of stimulus presentation was omitted as the NML profile within this interval contained lateralization of early cortical activity following stimulus onset. Phase I was defined from the start of the analysis window to the first transition (labeled t1), phase II from t1 to the second transition (t2), phase III from t2 to the third transition (t3) and phase IV from t3 to the end of the window. Within each interval, a regression line was fit to the NML profile and analysis of covariance (significance level $p = 0.01$) was performed on the slopes of the fitted functions. When slopes of adjacent functions were not significantly different, intervals were merged.

For statistical evaluation of inter-hemispheric amplitude differences in the LRP measure, mean LRP value within a time window subtending from movement onset to 100 ms following movement onset was calculated for every subject. Subsequently, calculated LRP values were examined by means of Wilcoxon's test of paired differences. A similar approach was employed for statistical evaluation of inter-hemispheric asymmetries in the NML measure. Five contiguous (500 ms) time windows were defined subtending from 2500 ms preceding stimulus offset, $t = -2.5$ s, to stimulus offset, $t = 0$ s. Mean NML values for each individual time window were evaluated by means of Wilcoxon's test. In addition, to assess differences in NML values between finger extension and eye movement, the entire stimulus presentation interval was sub-divided into six 500 ms time windows. Again for each individual time window, NML values were calculated. Mean NML amplitudes for both movement modalities were compared by means of Wilcoxon's matched pairs test. To account for multiple comparisons in the above outlined analyses, significant inter-hemispheric asymmetry was assumed when Wilcoxon's probability level was below $p = 0.01$.

Finally, for each electrode pair, the maximum non-motor specific lateralization value during stimulus presentation was determined. Maximum lateralization was calculated as the average amplitude across a 160 ms interval centred on the time at which NML amplitude was maximal. Maximum lateralization values were statistically

analysed by multivariate ANOVA with Anterior vs. Posterior (F', C' vs. C", O') and Electrode as within subject variables.

2.3. Results

2.3.1. Motor response latency

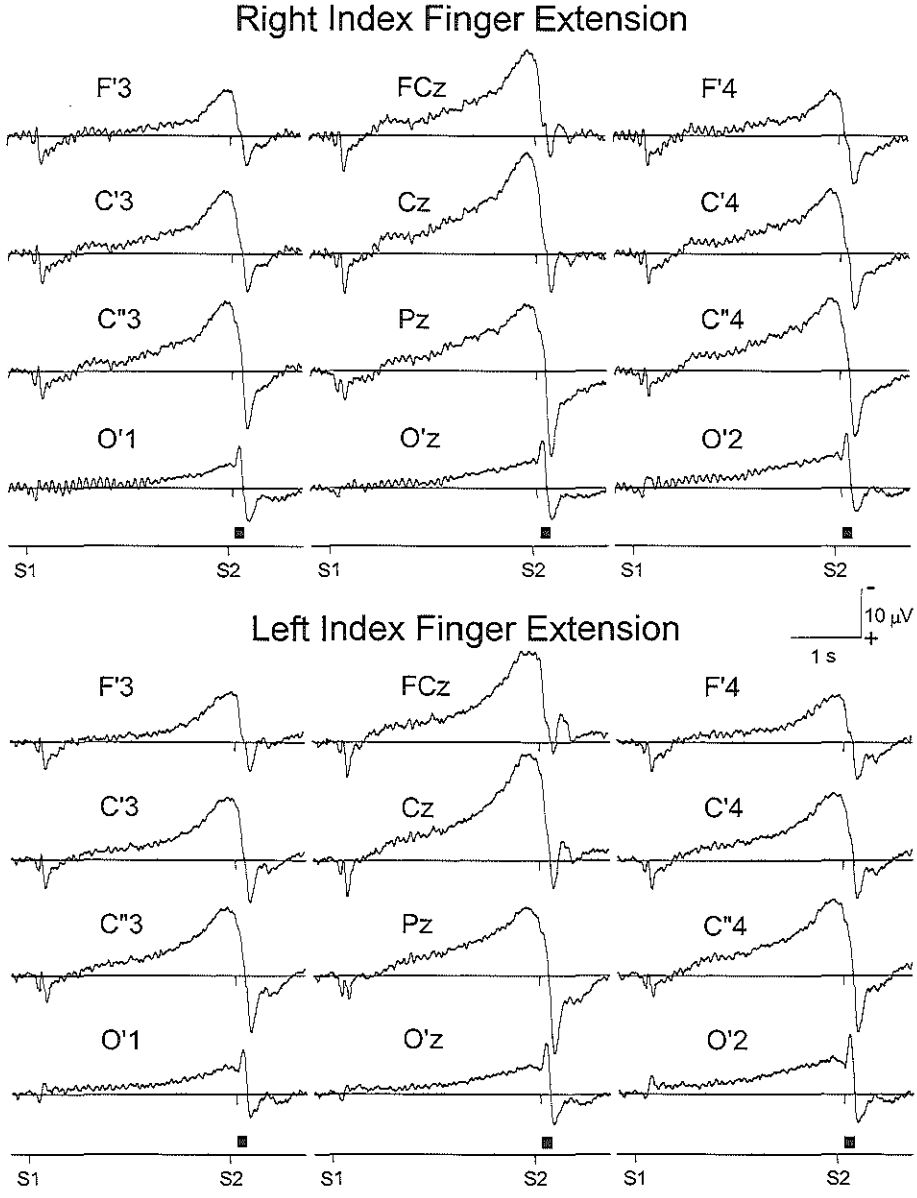
Mean motor response latencies for the four movement conditions are summarised in Table 1. In the statistical analysis, mean motor response latency in the finger extension tasks was significantly shorter compared with mean motor response latency in the eye movement tasks (factor Movement Modality; $F(1,9) = 29.55$, $p < 0.001$). No significant differences were found for mean latency of right compared with left finger extension or for mean latency of rightward compared with leftward saccades.

Right Finger Ext.	Left Finger Ext.	Saccades Rightward	Saccades Leftward
179 ± 23	167 ± 29	211 ± 22	209 ± 25

Table 1: *Mean motor response latencies (± standard error of the mean), averaged across mean response latencies for each individual subject, for the four movement conditions (right finger extension, left index finger extension, rightward saccadic eye movement and leftward saccadic eye movement).*

2.3.2. Event related potentials

In all subjects, robust event related cortical activity (ERPs) was recorded. Averages were calculated which included trials with response latency within 110.8 - 230.8 ms (170.8 ms ± 60.0 ms) for the right as well as left finger extension conditions and within 149.7 - 270.1 ms (209.9 ms ± 60.2 ms) for the right- as well as leftward saccadic eye movement conditions. Similar ERP profiles were obtained for all four movement conditions as illustrated in Figs. 2 and 3. The similarity of recorded ERPs for finger extension compared with eye movement is additionally demonstrated in Fig. 4, which, for midline electrode sites, depicts cortical response profiles averaged across subjects and across right and left finger extension (thin lines) as well as across right- and leftward saccades (bold lines). Note also that across movement modalities, the early cortical activity following the onset of the computer animation ($t = -3$ s) and subsequent contingent negative variation (CNV) are nearly identical.


Right Index Finger Extension
F'3
FCz
F'4
C'3
Cz
C'4
C"3
Pz
C"4
O'1
O'z
O'2
S1
S2
S1
S2
S1
S2
Left Index Finger Extension
10 µV
1 s
F'3
FCz
F'4
C'3
Cz
C'4
C"3
Pz
C"4
O'1
O'z
O'2
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S2
S1
S2
S1
S2

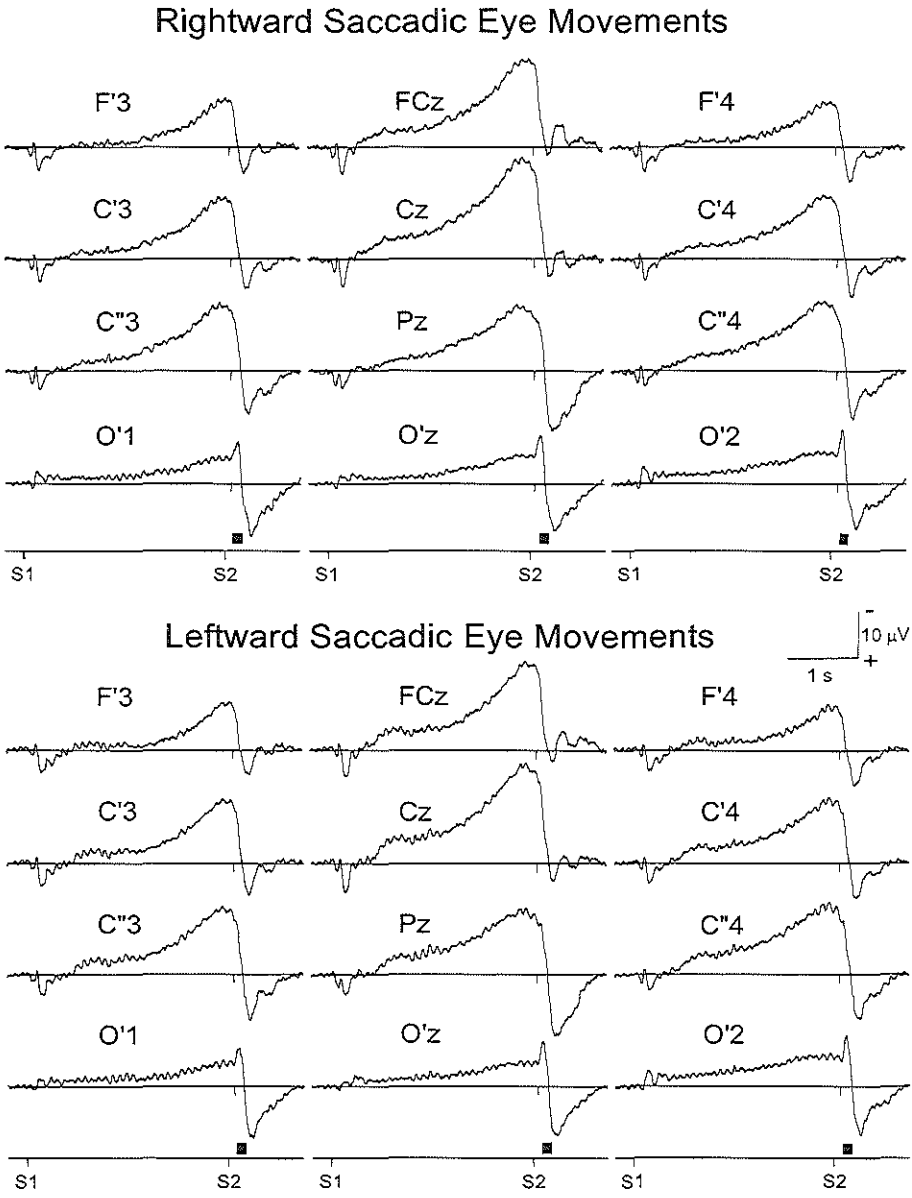
Rightward Saccadic Eye Movements
F'3
FCz
F'4
C'3
Cz
C'4
C"3
Pz
C"4
O'1
O'z
O'2
S1
S2
S1
S2
S1
S2
Leftward Saccadic Eye Movements
10 µV
1 s
F'3
FCz
F'4
C'3
Cz
C'4
C"3
Pz
C"4
O'1
O'z
O'2
S1
S2
S1
S2
S1
S2

Figure 2: *Event related potentials, averaged across subjects, during finger extension conditions. Upper ERP profiles: right index finger extension; lower ERP profiles: left index finger extension. Each trace represents the ERPs recorded at one of the twelve electrode sites. Traces are depicted following the montage in which the electrodes were positioned on the scalp. The averaged waveforms are derived from stimulus synchronized ERPs. Completion of the computer generated animation is at 0 s. Stimulus onset (S1) and onset of imperative color change (S2) are indicated below the occipital traces. Small horizontal bars following S2 illustrate range of movement onset. Scalp topography and amplitude versus time profiles of the recorded ERPs are comparable for left and right finger extension. Event related potentials also are similar at frontal (F'3, FCz, F'4), central (C'3, Cz, C'4 and C"3, C"4) and parietal (Pz) electrode sites. Largest ERP amplitude values are recorded at the vertex (Cz). For the occipital electrode sites (O'1, Oz, O'2), amplitude values are lowest and amplitude versus time profiles exhibit an approximately constant increase in cortical negativity during the entire CNV interval. There is no clear evidence for an isoelectrical plateau during the initial segment of the CNV interval (initial CNV) nor for the subsequent increase in negativity during the final period of the CNV interval (terminal CNV). In addition, at occipital sites following stimulus completion (t = 0 s) a relatively sharp negativity is evident. The latter, subsequently labeled N2", is largest over the right hemisphere (O'2) and is evoked by the imperative change in stimulus color at 100 ms prior to the offset of the computer animation (t = -100 ms). Note also the attenuation of rhythmical EEG activity during the final segment of the CNV interval, especially for the occipital electrode sites during right finger extension.*

Figure 3: *Event related potentials averaged across subjects during eye movement conditions. Upper ERP profiles: rightward saccadic eye movement; lower ERP profiles: leftward saccadic eye movement. Note that the topography and time-course of the averaged waveforms are comparable for right- and leftward saccadic eye movements and also are similar to the cortical activity recorded during right and left finger movement conditions (see Fig. 2). Statistical analysis revealed no significant differences in amplitude values of components identified in the ERPs, either between finger extension and saccadic eye movement or between right and left finger extension and between right- and leftward saccades. See also the legend of Fig. 2 for more detail.*

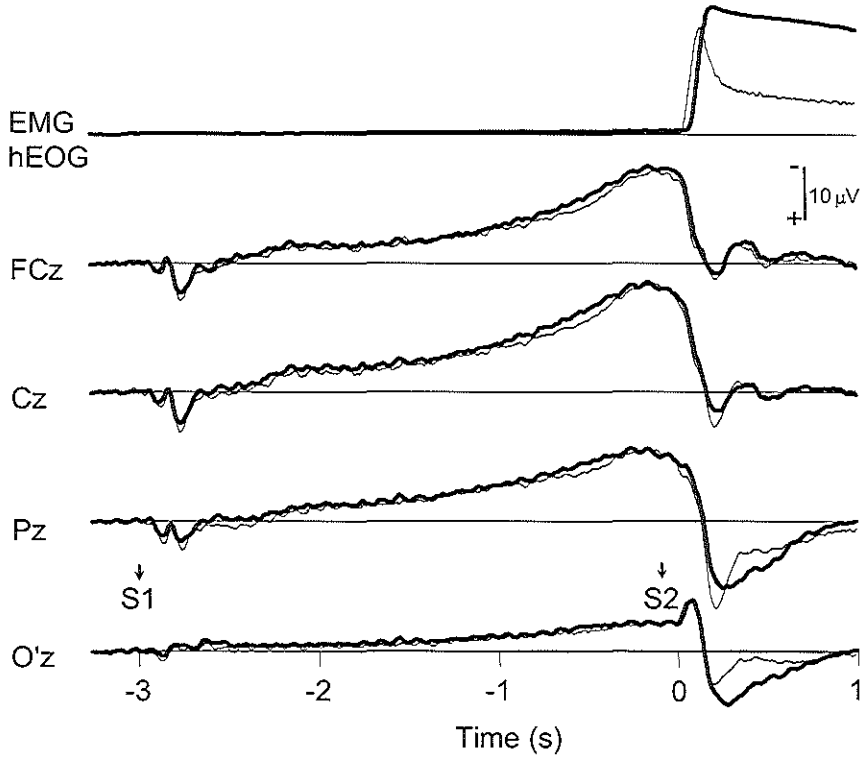

Figure 4: *ERPs recorded at four midline electrode sites (FCz, Cz, Pz, O'z), averaged across subjects and across right and left index finger extension conditions (thin lines) and right- and leftward saccadic eye movement conditions (bold lines), respectively. Depicted waveforms are derived from stimulus synchronized ERPs. Computer animation onset (S1) and onset of the imperative color change at 100 ms preceding stimulus completion (S2) are indicated. Note the similarity in amplitude versus time profiles of recorded cortical activity for the finger extension and saccadic eye movement conditions. The uppermost traces represent motor responses, i.e., electro-myographic (EMG) activity derived from the forearm index finger extension muscles for the finger extension conditions and horizontal electro-oculographic (EOG) activity for the eye movement conditions. Polarity of the EOG recorded during leftward saccadic eye movement was reversed prior to averaging the EOG traces for the right- and leftward saccadic eye movement conditions. Artefacts in the recorded ERPs as a result of the required saccades in the eye movement conditions were subtracted prior to averaging the ERPs recorded for right- and leftward eye movement (see methods section for more detail).*

Fig. 5 illustrates the components identified in the recorded cortical activity. ERPs at frontal (F'3, FCz, F'4), central (C'3, Cz, C'4 and C"3, C"4) and parietal (Pz) electrode sites consisted of early components P1 and N2 elicited by stimulus onset, followed by a positive component, labeled P3, and the CNV. The CNV could be subdivided into two components, an initial CNV (iCNV) and a late or terminal CNV (tCNV), in accordance with Weerts and Lang (1973). At the end of the pacing interval, the tCNV was terminated by a second positivity labeled P3'. At occipital sites (O'1, O'z, O'2), two visual evoked negativities were identified. The first, labeled N2', followed stimulus onset; the second, labeled N2", with more pronounced negativity, followed the imperative color change.

Amplitudes of the identified components typically were calculated in intervals subtending 40 ms centred on peak latency, i.e., the latency at which the amplitude of the component was maximal. Amplitude of CNV components were calculated over a larger time interval of 160 ms, which subtended from 960 to 1120 ms following stimulus onset (S1) for iCNV and across 160 ms centred on maximum response amplitude for tCNV. In general, amplitude values of ERP components were measured with respect to the directly preceding component (amplitude of component P3' was measured relative to total CNV amplitude, i.e., iCNV + tCNV). Components P1 and iCNV were measured with respect to the pre-stimulus baseline. Amplitude of N2" at occipital sites was measured relative to the mean ERP amplitude across a 100 ms interval preceding N2" onset. For statistical evaluation, all electrode sites were included in the analysis of P1, iCNV, tCNV and P3'. Occipital electrode sites (O'1, O'z, O'2) were excluded in the analysis of N2 and P3. Components N2' and N2" were examined at occipital electrode sites, only.

No significant inter- or intra-modality differences in amplitude of ERP components were found, neither between finger extension and saccadic eye movement, between right and left finger extension or between right- and leftward saccadic eye movements (for each component analysed, main factors Movement Modality and Movement Side: not significant). Further, for each component, the interaction Movement Modality by Movement Side also was not significant. A second analysis was performed for midline electrode sites (FCz, Cz, Pz, O'z) to examine the anterior versus posterior topography of the recorded cortical activity. For components P1, iCNV, tCNV and P3', midline topography was analysed with within-subject variables Anterior vs. Posterior (electrode sites FCz, Cz vs. Pz, O'z) and Electrode (2 levels). For components N2 and P3, the occipital site (O'z) was excluded and amplitude topography was examined with variable Electrode (3 levels: FCz, Cz, Pz), only. For early components P1 and N2, evoked by stimulus onset, variable Anterior vs. Posterior and variable Electrode, respectively, were not significant. For subsequent positive component P3, a significant main effect for variable Electrode was found ($F(2,18) = 41.08$, $p < 0.001$). Univariate F-tests indicated that P3 amplitude was largest at frontal-central sites FCz and Cz (FCz /Cz vs. Pz: $F(1,9) = 43.22$, $p < 0.001$). Component tCNV also was largest at frontal-central sites (variable Anterior vs. Posterior; tCNV: $F(1,9) = 27.40$, $p = 0.003$). For components iCNV and P3', a main effect of Anterior vs. Posterior was absent. Although component iCNV tended to be larger at frontal-central sites. For each individual component, variables Movement Modality, Movement Side and their interaction remained non-significant. Also, anterior/posterior topography of the cortical

response profiles was comparable for finger and eye movement conditions (interactions Movement Modality by Anterior vs. Posterior and Movement Modality by Electrode for components P1, iCNV, tCNV, P3' and components N2, P3, respectively: not significant). Table 2 lists, for each component, maximum amplitudes and electrode sites at which maximum amplitude was recorded (see column labeled Electrode). Also delineated are peak latencies, measured either with respect to stimulus onset (S1) or with respect to the onset of the imperative stimulus (S2) (see column labeled Reference).

Fig. 6, shows event related potentials for the 'Go/NoGo' control session (bold lines) and 'View Only' control session (thin lines). Response profiles in the initial segment of the CNV interval were comparable for both control sessions. Only for the electrode positioned at the vertex (Cz), was the initial CNV slightly larger for the 'Go/NoGo' session. No statistically significant differences were found comparing amplitudes of early ERP components (P1, N2, N2', P3 and iCNV) recorded in both control sessions (variable Control Session: not significant). Also, no significant differences were found when amplitudes were compared for each electrode site separately by means of paired t-tests ($p = 0.05$). Following the early ERP components, the tCNV developed in the 'Go/NoGo' session. In the 'View Only' session, negativity remained relatively constant and then subsequently decreased following stimulus offset.

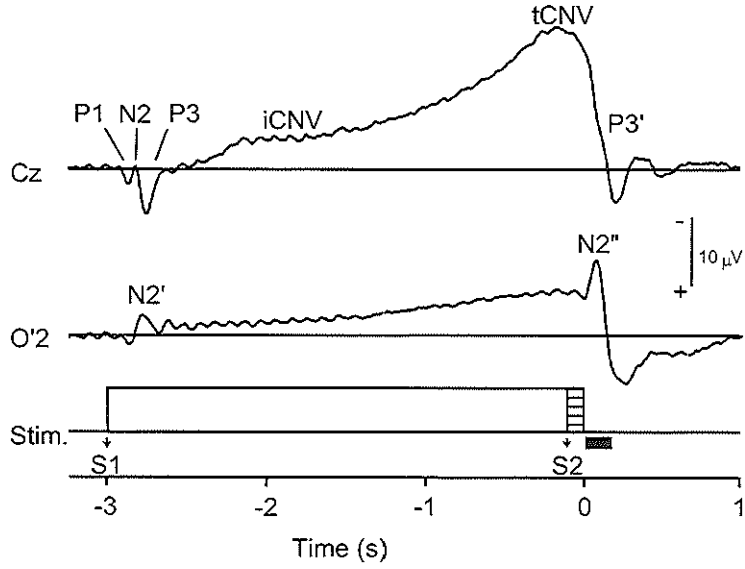

Figure 5: *Recorded ERP profiles averaged across subjects and across the four movement conditions (right index finger extension, left index finger extension, rightward saccadic eye movement, leftward saccadic eye movement) depicted for electrode sites at the vertex (Cz) and right occiput (O'2). Response components identified in the cortical activity recorded during execution of the experimental task are illustrated. In the upper trace (Cz), components P1, N2, P3, iCNV, tCNV and P3', evident in the ERPs recorded at the frontal, central and parietal electrode sites, are depicted. The lower trace (O'2) illustrates the averaged ERP waveforms recorded at occipital sites. Although to a lesser extent, components P1, CNV and P3' also are evident. The CNV is not readily subdivided into initial and terminal CNV components. Instead of the early components N2 and P3, a visual evoked negativity (N2') is more pronounced following stimulus onset. After stimulus completion, a similar negativity (N2") also is found. The latter is evoked by the onset of the imperative change in stimulus color. In the stimulus profile, onset of the computer animation (t = −3 s) is labeled S1. Onset of the imperative color change is labeled S2. The latter also is indicated by the dashed area starting at 100 ms prior to the offset of the computer animation (t = 0 s). The small dark horizontal bar below the stimulus profile indicates range of movement onset for finger extension and saccadic eye movement combined.*

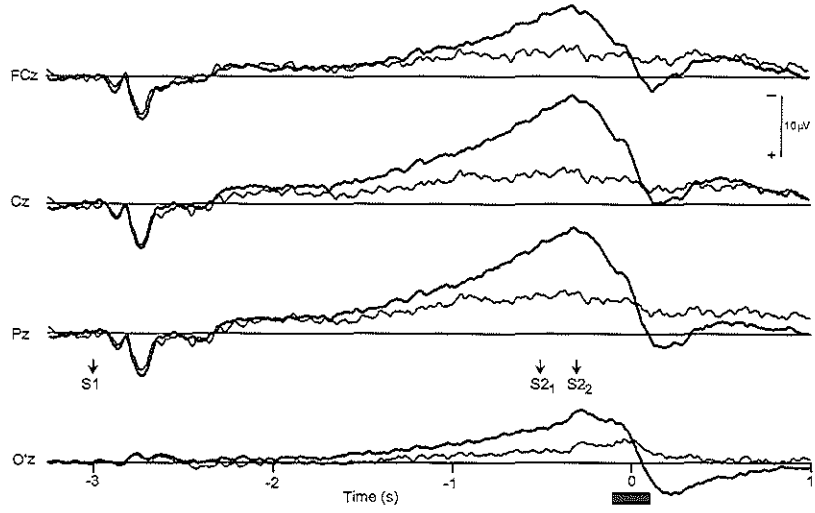

Figure 6: *Response profiles of cortical activity recorded in the control experiment, averaged across subjects and across 'Go' and 'NoGo' trials. Stimulus synchronized ERPs are depicted for midline electrode sites. The onset (labeled S1) and offset of the CNV stimulus occur at t = -3 s and t = 0 s, respectively. For both 'Go' as well as 'NoGo' trials, the change in stimulus color to green or red occurred at either 500 ms ($S2_1$) or 300 ms ($S2_2$) prior to completion of the half-circle sketch. Range of movement onset for saccades at 'Go' trials is illustrated by the bold horizontal bar below the time axis. Cortical response profiles recorded in the 'View Only' control condition are plotted as thin lines; bold lines represent cortical activity obtained in the 'Go/NoGo' control session. The 'Go/NoGo' control session is performed with rightward saccadic eye movements. No response requirements were imposed in the 'View Only' control session. The depicted waveforms illustrate that the event related potentials recorded during the initial segment of the CNV interval are comparable for the 'Go/NoGo' and 'View Only' control sessions. No statistically significant differences were found comparing amplitude values of the early components P1, N2, N2' and iCNV, following stimulus onset, in the ERPs recorded in either control conditions. Following the initial CNV (iCNV), a build up of cortical negativity in the 'Go/NoGo' control session reflects the terminal CNV (tCNV), while negativity remains approximately constant in the 'View Only' session.*

Component	Amplitude (μV)	Electrode	Latency (ms)	Reference
P1	3.8 ± 0.9	Pz	143 ± 7	S1
N2	-4.0 ± 0.7	C"3	179 ± 2	S1
P3	7.6 ± 0.9	Cz	240 ± 4	S1
iCNV	-4.3 ± 0.6	Cz	900 - 1500[1]	S1
tCNV	-17.2 ± 0.7	Cz	-37 ± 21	S2
P3'	28.7 ± 2.7	Pz	326 ± 25	S2
N2'	-4.9 ± 0.4	O'2	212 ± 4	S1
N2"	-5.3 ± 0.5	O'2	193 ± 10	S2

[1] approximate latency range as iCNV resembles an isoelectrical plateau

Table 2: *Maximum amplitude values and accompanying latencies of components evident in the recorded event related potentials. Amplitude and latency data depicted are mean values (± standard deviation), averaged across the amplitude and latency values determined from the ERPs, averaged across subjects, in each individual movement condition. Column Electrode indicates the electrode site at which the respective maximum amplitude values were recorded; column Reference indicates whether component latency was measured relative to the onset of the computer animation (S1) or to the onset of the imperative color change (S2).*

2.3.3. Lateralized readiness potential

Fig. 7 shows LRP profiles aligned on response onset (t = 0 s), for finger extension (thin lines) and saccadic eye movements (bold lines). For finger extension, a preponderance of cortical negativity over the contralateral hemisphere in the LRP profiles started at 510 and 480 ms prior to movement onset (t = 0 s) over motor (C') and sensorimotor (C") areas, respectively. The identified onsets of lateralization development are depicted by vertical lines in Fig. 7. Visual inspection indicated that the initial slow build up of hemispheric asymmetry was followed by a more rapid increase at about 40 ms preceding finger extension onset. Inter-hemispheric asymmetry during the initial 100 ms following movement onset was significant over motor (C') as well sensorimotor (C") areas. In contrast, during eye movement, an increase of cortical response negativity over the hemisphere contralateral to saccade direction was not found. Significant inter-hemispheric lateralizations also were absent. As an aside, note the sharp peak at movement onset (t = 0 s) detectable in the LRP for eye movement which is most pronounced for the LRPs at frontal and central electrode sites (F', C' and C"). The latter reflects an artefact due to the spike potential, generally attributed to the

activity of ocular motor muscles (Becker et al., 1972; Kurtzberg and Vaughan, 1982).

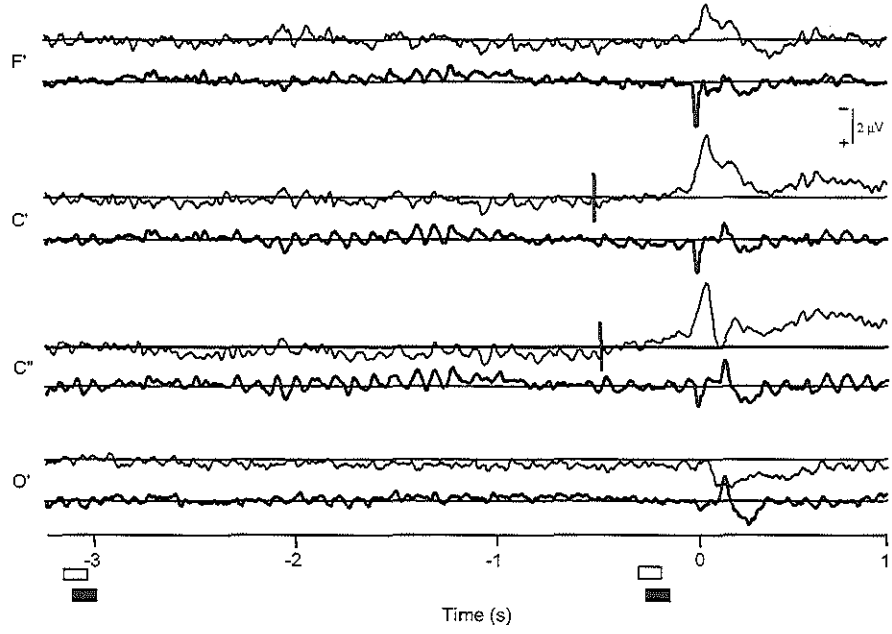

Figure 7: *Lateralized readiness potentials (LRP) derived from the recorded cortical activity, aligned on motor response onset (t = 0 s), averaged across subjects. From top to bottom: F' = F'3 vs. F'4; C' = C'3 vs. C'4; C'' = C''3 vs. C''4 and O' = O'1 vs. O'2. Horizontal bars below the time axis represent the range of stimulus and imperative color change onset for finger extension (dark bars) and saccadic eye movements (light bars), respectively. Thin lined traces represent LRP profiles for finger extension, bold traces depict LRP profiles for saccadic eye movement. For clarity, LRPs obtained for the finger extension and saccadic eye movement conditions are plotted on separate axes. Negative values of the LRP profiles (plotted upward) indicate a preponderance of cortical negativity over the hemisphere contralateral to the side of the movement. For finger extension, a slow build up of enhanced cortical negativity over the contralateral cerebral hemisphere is evident at about 500 ms preceding movement onset across central cortical areas (C' and C''). Onsets of identified inter-hemispheric lateralization development are depicted by vertical lines. Hemispheric lateralization, when present, increases more rapidly at about 40 ms prior to movement onset and eventually reaches a maximum during movement onset. In the LRP for eye movements, movement related lateralizations are not visible.*

2.3.4. Non-motor related lateralization

Fig. 8 shows non-motor related lateralization profiles as obtained in finger extension (thin lines) and saccadic eye movements (bold lines). For both movement modalities, lateralization profiles were similar and no significant differences were found when NML profiles were compared with Wilcoxon's matched pairs test. For subsequent analysis, calculation of the NML profiles for ERPs averaged across finger extension and saccades was effected. The prominent feature in the NML profiles was a preponderance of cortical slow wave negativity at right hemispheric electrode sites during stimulus presentation.

Vertical lines in Fig. 8 illustrate the separate phases of inter-hemispheric asymmetry development identified. An initial increase in right hemispheric asymmetry following stimulus onset (phase I) was succeeded by a period in which asymmetry development slowed down (phase II) at -1922 ms for electrode sites F' and C' and at -1930 ms for C". A concurrent change in rate of asymmetry development was not evident for the occipital electrodes (O'). An approximately constant level of asymmetry (phase III) was attained at -1047 ms for sites F' and C', and at about 300 ms earlier for C" (t = -1316 ms). For the occipital sites, a deceleration of asymmetry development was evident at -1316 ms, however, a constant level of asymmetry was not attained. Finally, hemispheric asymmetry resolved (phase IV) at -465 ms for electrodes positioned over the frontal eye fields (F') and primary motor cortex (C'), at -449 ms over the sensorimotor cortex (C") and at -484 ms over occipital sites (O'). The slopes of the regression functions fitted to the NML profiles in the time windows defined by each phase, are listed in Table 3; for each fitted function, the residual standard deviation was below 0.25 μV. The right column of Table 3 (column labeled Max. Lat.) lists maximal non-motor related lateralization values. In general, maximum NML values were recorded at the transition between phase III and phase IV. Right hemispheric asymmetry was largest at occipital sites (O' = O'1 vs. O'2) and decreased in anterior direction. In the statistical analysis, a main effect of Anterior vs. Posterior ($F(1,9) = 5.81$, $p = 0.039$) indicated that lateralization was significantly larger at posterior electrode sites (C" = C"3 vs. C"4 and O' = O'1 vs. O'2).

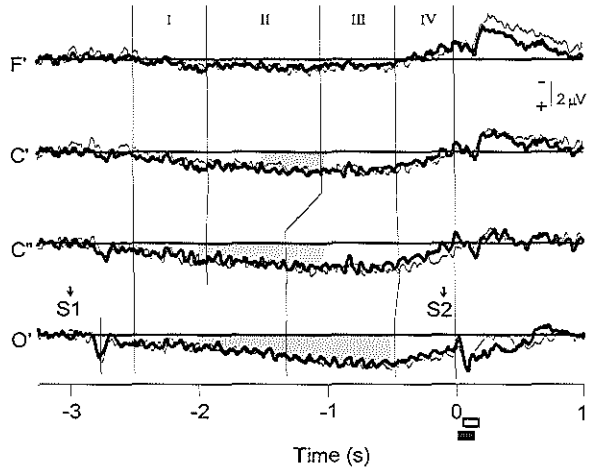

Figure 8: *Non-motor related lateralization (NML) waveforms, derived from stimulus aligned ERPs, averaged across subjects and derived for homologous electrode sites positioned over the left and right hemispheres. From top to bottom: F' = F'3 vs. F'4; C' = C'3 vs. C'4; C'' = C''3 vs. C''4 and O' = O'1 vs. O'2. Thin traces represent NML profiles obtained for right and left index finger extension; bold traces depict the NML profiles for right- and leftward saccadic eye movement. The stimulus presentation interval extends from −3 s to 0 s. Stimulus onset (S1) occurs at −3 s. Onset of imperative color change (S2) also is depicted. Horizontal bars below the time axis indicate range of movement onset for finger extension (dark bar) and eye movement (light bar), respectively. Note that positive values of the NML profiles (plotted downward) indicate a preponderance of cortical negativity over the right hemisphere. In the resultant NML profiles, a right hemispheric lateralization is evident during the CNV interval due, most likely, to presentation of the stimulus in the left visual field. Lateralization of cortical negativity is largest over the occipital cortex (O'). The amplitude versus time profiles and anterior-posterior topography of non-motor lateralization is comparable for the finger extension and saccadic eye movement conditions with no significant differences between the NML profiles obtained for either movement modalities. NML profiles were calculated from the recorded ERPs averaged across finger extension and eye movement conditions. Grey areas mark the time windows during which inter-hemispheric lateralization was significant in the NML profiles for finger extension and saccade conditions, combined. Vertical lines at −2.5 s and 0 s, respectively define the time window in which the identification of separate phases of inter-hemispheric asymmetry development was effected. Additional vertical lines define the separate phases (depicted as I, II, III and IV) of inter-hemispheric asymmetry development identified for each electrode pair. Note that for occipital electrode pair (O'), the vertical line separating phases I and II is absent. The small vertical line drawn for the occipital electrode pair at about 200 ms following onset of computer animation marks the right hemispheric lateralization associated with visual evoked negativity N2'.*

	Slope (μV/s)				Max. Lat. (μV)
	I	II	III	IV	
F'	1.42 ± 0.10	0.47 ± 0.05	0.01 ± 0.10	-2.59 ± 0.14	0.39 ± 2.01
C'	1.53 ± 0.09	0.76 ± 0.04	0.24 ± 0.09	-2.86 ± 0.14	1.28 ± 2.54
C"	1.65 ± 0.11	0.57 ± 0.07	-0.05 ± 0.05	-3.05 ± 0.17	1.72 ± 2.41
O'	0.99 ± 0.04		0.67 ± 0.05	-2.11 ± 0.09	2.21 ± 1.86

Table 3: *Calculated slopes and maximum lateralization values (± standard deviation) of non-motor related lateralization profiles derived from recorded ERPs averaged across finger extension and eye movement conditions. Positive values depict right hemispheric lateralization. Columns I, II, III and IV list the slopes of the regression functions fitted to the NML profile in the identified individual phases of lateralization development during stimulus presentation. In column Max. Lat., maximum lateralization values for the NML profile calculated at each electrode pair are shown. For the occipital electrode sites, slopes of the NML profiles in phase I and II were not significantly different and were therefore merged.*

2.4. Discussion

In the present study, event related potentials were recorded in a contingent negative variation (CNV) task. Following an imperative stimulus (S2), an overt response was either executed or withheld (Go/NoGo task). The experimental task was performed with four movement conditions; right index finger extension, left index finger extension, rightward saccadic eye movement and leftward saccadic eye movement.

The results show that amplitude versus time profiles of the recorded event related potentials (ERPs) were comparable between either movement modality and between either movement side. Assessment of movement related cortical activity using the lateralized readiness potential (LRP) showed a build up of contralaterally enhanced cortical negativity preceding finger movements. Movement related lateralization was largest over the central cortex (electrode sites C'3, Cz, C'4, C"3, C"4). Comparable lateralizations were absent prior to saccadic eye movements. Evaluation of non-motor specific inter-hemispheric lateralization by means of the non-motor lateralization (NML) measure revealed a preponderance of non-motor related cortical response negativity across the right hemisphere. The asymmetry was largest over the posterior cortex and was comparable in both finger extension and saccadic eye movement conditions.

2.4.1. Motor response latency

The stimulus configuration employed in the present experiment provided precise information of the time at which the imperative stimulus occurred, thus facilitating

response latencies for both movement modalities. Nevertheless, mean response latencies during finger extension were significantly shorter compared with eye movements. The inter-modality difference in response latency may, largely, be explained by the dissimilar measures of response onset applied in the two test conditions. That is, in the finger extension conditions, response onset was defined as the onset of movement related muscle activity, while in the eye movement conditions, response onset was specified as the onset of the saccade. No significant inter-modality differences were found comparing response latency, e.g., between right and left finger extension or between right- and leftward saccades.

2.4.2. Event related potentials

Early ERP components P1, N2, N2', P3 and iCNV also were present in the ERPs obtained in the control 'View Only' experiment in which a motor action was not required. This finding indicates that the early response components primarily reflect non-motor specific cortical activity elicited by stimulus onset. In particular, it has been suggested that the early CNV component (iCNV) is either an afterwave related to the processing of stimulus onset or possibly an orienting response (Grey Walter et al., 1964; Loveless, 1976; Gaillard, 1977; Rohrbaugh et al., 1984).

In the present study, during the final segment of the stimulus presentation interval, the terminal CNV (tCNV) developed in the 'Go/NoGo' response conditions. Time course and amplitude of the tCNV was comparable for the finger extension and eye movement conditions. The finding of similar amplitude values contradicts the findings of Wauschkun et al. (1997) who reported CNV amplitudes to be larger during finger movement. Response latencies herein also were longer for eye movement compared with finger movement. Presumably, relatively more effort was required to respond within the imposed reaction time limit in the eye movement condition. The greater 'workload' also may have augmented CNV amplitude values as it has been reported that CNV amplitude increases with growing task effort and task complexity (McCallum and Papakostopoulos, 1973; McCallum and Pocock, 1983).

Results of the present study agree with the investigation of Thickbroom and Mastaglia (1990) who found the topography and time course of cortical pre-movement negativity comparable for self-initiated finger and saccadic eye movements. Thickbroom and Mastaglia suggested that the observed pre-movement negativity primarily represents non-movement specific cortical processing. It should be noted, however, that finger and eye representations within the frontal lobe of the cerebral cortex are in close proximity to each other. Within lateral regions of the frontal lobe, the eye movement representation (frontal eye fields) also includes an area adjacent to the hand representation within the primary motor cortex (M1). Analogously for medial regions of the frontal lobe, hand and eye representation in the supplementary motor area (SMA) also are in close proximity to each other (Sweeny et al., 1996). Specifically, the supplementary eye fields (SEF) identified in the rostral portion of the SMA (Schlag and Schlag-Rey, 1987) may contribute to motor preparation preceding eye movements. In addition, a CNV paradigm also evokes cortical activity within the (pre-)frontal cortex (Hamano et al., 1997). Thus, analysis of averaged ERPs only may be insufficient to spatially distinguish various frontal responses. Head volume conductor effects may

underlie the similar spatiotemporal evolution of recorded ERPs between either movement modality. Future studies with use of larger electrode arrays and application of the Laplacian derivation to the recorded ERPs (Biggins et al., 1991; Biggins et al., 1992; Biggins and Fein, 1993; Perrin, 1992; Pasqual-Marqui, 1993, Lagerlund et al., 1995), dipole modeling (e.g., Böcker et al. 1994) or application of the magneto-encephalogram (MEG: e.g., Hamalainen, 1992) in addition to EEG, which reduces the influence of head volume conduction, may help to distinguish the contribution of individual cortical areas.

2.4.3. Lateralized readiness potential

In the present study, during finger movement, a preponderance of cortical activity over the hemisphere contralateral to the active finger was evident in the LRP profiles across central cortical areas (C' and C"). However, movement related lateralizations were not observed in the LRP associated with saccadic eye movement. These latter results are in agreement with the study of Wauschkun et al. (1997). Note also for the experimental paradigm described herein, that the probability for finding pre-saccadic inter-hemispheric ERP asymmetries was optimized. That is, compared to Wauschkun and colleagues, in the present study an electrode montage was employed that included cortical areas where the frontal eye fields have been localized (Sweeney et al., 1996). In addition, in the current study, the lateralized readiness potential was derived from response synchronized instead of stimulus synchronized ERPs (Sommer et al., 1994). Finally, in the present study in contrast to Wauschkun et al. (1997), amplitude values of event related potentials were comparable for either movement modality; saccade related lateralization nonetheless was not recorded.

Studies on inter-hemispheric asymmetry of the readiness potential (RP) indicate that movement related lateralizations appear independent of movement attributes such as movement force (Kutas and Donchin, 1977; Becker and Kristeva, 1980; Kristeva et al., 1990; Sommer et al., 1994), movement direction (extension vs. flexion) (Deecke et al., 1980) and/or reaction time (Hackley and Miller, 1995). One exception is reported by Hackley and Miller (1989, 1995), who observed an enhancement of LRP amplitude preceding complex, compared with simple, finger movements. Accordingly, it has been suggested that movement related lateralization merely reflects the selection of response alternatives, e.g., body side (right vs. left hand) or extremity (hand vs. foot), (Gratton et al., 1988; Sommer et al., 1994). Therefore, lateralization may be absent for saccades, as there are no comparable alternatives available for conjugate eye movements. As referred to previously by Wauschkun et al. (1997), the absence of lateralized pre-saccadic cortical activity appears to be in conflict with studies on electrical stimulation of the cerebral cortex in which stimulation of the frontal eye fields (FEF; Godoy et al., 1990) and supplementary eye fields (SEF; Lim et al., 1994) elicits saccadic eye movements to the contralateral side. As a caveat, however, it should be pointed out that for eye movements generated under more natural circumstances, involved cortical and sub-cortical pathways and/or degree of activation of ocular motor areas in either cerebral hemisphere may well be distinct from saccades generated in the artificial condition induced by electrical stimulation.

Alternatively, in the present study a possible though slight functional asymmetry in the activation of ocular motor areas in both hemispheres might have been masked due

to head volume conductor effects. For example, Böcker et al. (1994) found a relatively small contralateral preponderance of scalp recorded cortical activity preceding unilateral finger movement. In contrast, Böcker and colleagues found much larger inter-hemispheric asymmetry following spatio-temporal dipole modeling of the ERPs. Thus, the likelihood of finding saccade related lateralization may be enhanced when dedicated computerized techniques are used which reduce the influence of head volume conduction (i.e., Laplacian transform).

Further, in the present study no significant differences between finger and eye movement were found in comparing mean amplitudes of component P3' following the imperative stimulus. Kok (1986) suggested that compared with 'NoGo' stimuli, the amplitude of the 'P300' following 'Go' stimuli may be reduced due to temporal overlap with a negative motor potential. When temporal overlap is taken into account, a larger amplitude of the 'P300' during eye movement compared with finger movement may be expected when eye movement specific cortical activity is, in fact, absent. The lack of such an amplitude effect in the present study suggests that, despite the absence of saccade related lateralizations, a contribution of cortical ocular motor areas to the recorded ERPs, in analogy with the negative motor potential in finger movement, cannot be completely excluded.

2.4.4. Non-motor related lateralization

For finger movement, an fMRI study by Kim et al. (1993) has shown that with respect to the right primary motor cortex, the left primary motor cortex plays a prominent role in the control of ipsilateral finger movement. When motor specific lateralization for left versus right finger movement is not comparable, the NML profiles will include a motor related component. As an aside, when lateralization of cortical activity preceding left finger movement is less pronounced, the LRP also will be inaccurate. The LRP would indicate a slightly higher motor related asymmetry, compared with the asymmetry actually present, for left finger movement and a correspondingly smaller asymmetry for right finger movement. The finding of similar NML profiles for finger and eye movement, in combination with the observation that movement related lateralization was present in finger extension only, indicates that for finger extension, motor related lateralization was comparable for a right or left side movement and thus cancelled in the NML profiles. The latter validates the interpretation in the present study of the calculated NML profiles as representing non-motor related lateralization.

With regard to the posterior distribution of the NML profiles, the observed lateralization appears to reflect primary sensory processing, particularly as the left visual hemi-field, in which the stimulus was presented, projects directly to the right visual cortex. For example, it is well documented that half-field visual stimulation, in particular for the earlier components of the visual evoked response to luminance and pattern onset, results in contralateral response lateralization (Jeffreys and Axford, 1972; Shagass et al., 1976; Apkarian et al., 1984; Butler et al., 1987). In addition, non-motor lateralization may, in fact, be associated with the directed attention potential (DAP), attributed to parietal lobe activity as reported in studies of Lang et al. (1984) and Deecke et al. (1985). Regarding hemispheric specialization for directed visuospatial

attention, previous ERP studies also indicate that the neural system accounting for attention shift seems to be organized symmetrically. That is, a preponderance of cortical activity over the hemisphere contralateral to the stimulated hemi-field has been recorded, for attention directed to the left as well as for attention directed to the right visual hemi-field (Luck and Hillyard, 1994; Yamaguchi et al., 1994; Yamaguchi et al., 1995; Wascher and Wauschkun, 1996). For future related experiments however, test conditions in which the CNV stimulus is presented in the right visual field as well as the left, should be implemented.

In the study reported herein, the time course of right-hemispheric lateralization was readily subdivided into four phases (Fig. 8; Table 3). Attention to the stimulus is likely to be strongest immediately preceding the imperative color change. Thus, the early resolution of right-hemispheric lateralization during phase IV appears to contradict the assumption of NML profiles as reflecting visuospatial attention. Alternatively, the observed decrease in lateralization also may reflect a shift of attentional focus from the peripheral visual field to the midline. When a spotlight analogy of selective processing of visual information by the attentional system is adopted (Treisman and Gormican, 1988), it may be assumed that the attentional focus is tracking a particular section of the stimulus. Accordingly, the focus of attention may initially be close to the vertical meridian and then when the half-circle builds up, extends into the left visual field. Finally, after the circle slice has crossed the horizontal meridian, attention returns to the vertical midline. It also has been shown that reaction times to visual stimuli presented near central fixation are faster than reaction times to eccentric stimuli (Shulman et al., 1979). Therefore, the observed asymmetry profiles also may be related to the strategy of first attending to the initial progress of the stimulus in the peripheral visual field and then shifting attentional focus to the field near central fixation when the imperative color change is imminent. As an aside, there is also evidence that the right hemisphere is biased toward global and the left hemisphere toward local attention processing (e.g., Sergent, 1982; Robertson and Delis, 1986; Fink et al., 1996). However, the exact relationship between lateralized hemispheric involvement and local versus global processing is yet to be resolved (e.g., Boles and Karner, 1996; Fink et al., 1997). Following the supposition of right hemisphere global and left hemisphere local processing, a final possible argument is that in the initial segment of the CNV interval, the right hemisphere was dominant, monitoring the general progress of the stimulus, whereas, at a later stage, the left hemisphere became more involved as the imperative color change required processing.

2.4.5. Conclusion

The results of the present study suggest that previously reported inter-hemispheric lateralization of cortical activity preceding self-initiated saccadic eye movements may be of non-motor origin. In particular, the latter may be associated with a covert shift of visuospatial attention toward the saccadic target preceding saccade onset. Depending on saccade direction, attention is shifted either to the right or left visual hemi-field. Therefore, hemispheric cortical response dominance may switch dependent on saccade direction and concomitant non-motor related lateralizations also may modify the lateralized readiness potential. The aforementioned visuospatial attention shifts are suppressed in a CNV paradigm. Future studies employing

neuroimaging approaches with higher spatial resolution compared with conventional EEG technologies may promise new insights into issues concerning cortical activity and motor versus non-motor function.

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3

Motor response inhibition in finger movement and saccadic eye movement: a comparative study

Abstract

To study cortical potentials associated with suppression of intended motor actions, electro-encephalographic activity was recorded in a Go/NoGo reaction time paradigm.

Subjects viewed computer generated pacing stimuli which provided information concerning the time at which an imperative Go/NoGo signal occurred. A motor response was required following Go stimuli while motor inhibition was required following NoGo stimuli. To examine whether previously reported 'Go/NoGo effects' on event related potential (ERP) components may be generalized across movement modalities, the present experimental paradigm was performed with either finger movement or saccadic eye movement as required response.

For both movement modalities, comparable differences in morphology, amplitude and scalp topography of ERP components were observed between Go trials, with proper movement execution, and NoGo trials, with complete suppression of motor activity. In addition, for either movement modality a similar 'error related negativity' (ERN) was found for NoGo trials in which motor activity was present.

The results of the present study suggest that cortical activity underlying the Go/NoGo differences in ERP components represent general cortical processing associated with detection and/or suppression of inappropriate response behaviour, independent of movement modality.

3.1. Introduction

Scalp recorded cortical activity associated with motor response inhibition can readily be examined by comparing event related potentials following stimuli that either command or prohibit a specific motor response. For example, in a Go/NoGo reaction time paradigm, a pre-defined motor response is required following Go stimuli while the response is to be withheld following NoGo stimuli (Karlin et al., 1970). Several Go/NoGo studies report an enhancement in amplitude of the late positivity 'P300', referred to also as 'P3', on NoGo trials compared with Go trials (Karlin et al., 1970; Hillyard et al., 1976; Simson et al., 1977; Pfefferbaum et al., 1985; Pfefferbaum and Ford., 1988; Kok, 1986; Jodo and Inou, 1990; Roberts et al., 1994). Several of these studies (e.g., Karlin et al., 1970; Hillyard et al., 1976; Simson et al., 1977; Pfefferbaum et al., 1985; Pfefferbaum and Ford., 1988; Roberts et al., 1994) also report that component 'P300' following NoGo stimuli is most pronounced at frontal-central scalp sites, while the 'P300' elicited by Go stimuli dominates at parietal sites. Latency of component 'P300' also is generally found prolonged on NoGo trials (e.g., Simson et al., 1977; Pfefferbaum et al., 1985; Pfefferbaum and Ford., 1988; Roberts et al., 1994). The Go/NoGo effect on component 'P300' has been associated with cortical processing related to motor response inhibition (Karlin et al., 1970; Roberts et al., 1994).

Concomitant to the 'P300' Go/NoGo effect, several studies report a negative component, typically labeled N2, which is most pronounced following NoGo stimuli (Simson et al., 1977; Eimer, 1993; Jodo and Kayama, 1992; Jodo and Inoue, 1990; Kok, 1986; Pfefferbaum et al., 1985; Gemba and Sasaki, 1989; Naito and Matsumura, 1994a,b; Falkenstein et al., 1995; Naito and Matsumura, 1996). Component N2 is reported as maximal at frontal scalp sites with a latency of about 200-300 ms relative to the onset of the Go/NoGo stimulus. As for the 'P300' Go/NoGo effect, the N2 Go/NoGo effect also has been related to inhibition of inappropriately initiated responses.

An additional negative component also is observed during NoGo 'error' trials, i.e., NoGo trials in which the motor response is erroneously executed (Falkenstein et al., 1995; Naito and Matsumura, 1994b; Kopp et al., 1996b; Scheffers et al., 1996). This component has been labeled 'error-related negativity' (ERN) (Gehring et al., 1993) or 'error negativity' (N_e) (Falkenstein et al., 1991). In general, amplitude of the ERN/N_e is reported to be enhanced compared with component N2 derived from 'correct' NoGo trials (e.g., Naito and Matsumura, 1994b). However, morphology, latency and scalp topography of the N2 and ERN/N_e are reported to be comparable (Falkenstein et al., 1995). Related studies suggest that the ERN/N_e on error trials may be associated with error-processing mechanisms (e.g., Falkenstein et al., 1991; Gehring et al., 1993; Scheffers et al., 1996).

In chapter 2 of this thesis, cortical activity was recorded in a contingent negative variation (CNV) paradigm. Computer generated pacing stimuli were presented that also provided information regarding the time at which a Go/NoGo stimulus appeared. In the previous study of chapter 2, analysis was restricted to cortical activity recorded on 'Go' trials with concentration on recorded event related potentials (ERPs) during the time interval between onset of the pacing stimulus and onset of the imperative Go/NoGo stimulus. In contrast, the present study concentrates primarily on ERPs recorded

following the imperative signal. In particular, cortical response profiles following Go and NoGo stimuli were compared to examine amplitude, latency and scalp topography of ERP components associated with suppression of intended actions. Generally, previous Go/NoGo studies focused on suppression of intended finger movement (see e.g., Jodo and Inoue, 1990; Roberts et al., 1994; Falkenstein et al., 1995). However, in the present study, cortical activity was evaluated during performance of the Go/NoGo test paradigm with either finger movement or saccadic eye movement as required action. Event related potentials following Go and NoGo stimuli for finger and eye movement conditions were compared to examine whether the 'Go/NoGo effects' on ERP components as reported in previous studies (e.g., Naito and Matsumura, 1994a,b; Roberts et al., 1994; Kopp et al., 1996b; Scheffers et al.,1996) are characteristic for hand movement or whether comparable effects are found across movement modalities.

3.2. Methods and Materials

The subject group, experimental protocol and procedures for recording electrophysiological activity are briefly described; for more detail, see chapter 2.

3.2.1. Subjects

A total of ten, right-handed, subjects participated in the study, including 7 males and three females (age range 22-51, mean age 31.3 yrs). Informed consent was obtained from each subject; experimental protocols were approved by the ethics committee of the Erasmus University Medical Faculty.

3.2.2. Stimulus and procedure

Subjects sat in a comfortable chair, with head support, facing a computer screen positioned at a distance of 81 cm. In the centre of the screen a fixation target (radius 0.15°) was displayed. During a cartoon animation of three seconds duration, the left half of a circle (radius 4.5°), centred on the fixation point, was drawn (Fig. 1). Subjects were instructed to maintain central fixation during the computer animation. At 100 ms prior to stimulus completion, a change in circle fill color from grey to green or red, either color occurring at random with 50% probability, signaled whether subjects were to initiate (green) or withhold (red) a given motor response. At two and a half seconds following each trial, visual feedback was provided indicating whether or not subject reaction time was within 200 ms following imperative color change (S2) onset. The time interval between subsequent trials was randomized between four and ten seconds.

The experimental protocol was performed with four movement conditions conducted in separate test sessions, including right finger extension, left finger extension, rightward saccadic eye movement and leftward saccadic eye movement. Each session consisted of 7 blocks of 3 minutes each; session order was counterbalanced across subjects. In the eye movement conditions, two small filled circles (radius 0.3°) presented permanently at 8.5° left and right from the central fixation point served as saccadic targets.

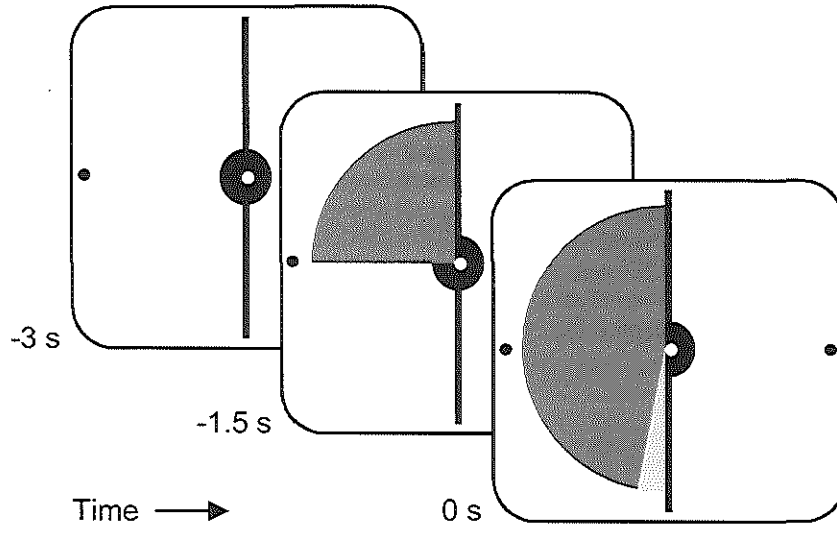


Figure 1: *Visual stimulus consisting of a computer drawn half-circle. Depicted are onset of the computer animation (S1) at −3 s, initial half of the computer sketch at −1.5 s and final completion of the animation at 0 s. Subject is required to maintain central fixation during the entire computer animation. The initial circle fill color is grey, but at 100 ms preceding stimulus completion (S2), the final circle segment is drawn in green or red, at random with 50 % probability for either color occurring. Subjects are instructed to initiate (green) or to withhold (red) a pre-defined motor response. Note the two saccadic targets displayed simultaneously right and left of central fixation, along the horizontal meridian.*

3.2.3. Recording

Electro-encephalographic (EEG) activity was recorded from twelve scalp sites, referred to linked earlobe electrodes. Electrodes Cz and Pz were positioned according to the standard 10-20 system (Jasper, 1958). Site FCz was positioned midway between scalp sites Cz and Fz of the 10-20 system (e.g., Lang et al., 1984; Naito and Matsumura, 1994a) and electrodes C'3, C'4, and C''3, C''4 were placed respectively 1 cm anterior and 2 cm posterior to landmarks C3 and C4 of the 10-20 system (e.g., Grünewald-Zuberbier et al., 1981); sites F'3 and F'4 were located 1 cm lateral and 2 cm anterior to C'3, C'4 (Sweeney et al., 1996). Finally, sites O'z, O'1 and O'2 were positioned 1 cm above the inion on the midline (O'z) and at 5 cm left (O'1) and right (O'2) of the midline (Harding et al., 1996). Electro-myographic activity (EMG) was recorded from two electrode pairs covering left and right index finger extensor muscles. Electro-oculography (EOG) was recorded, in bipolar derivation, from electrodes placed at the outer canthi of both eyes. To control for eye blinks and vertical eye movements, an additional electrode was positioned above the nasion and referred to the electrode at the right outer canthus. EEG

and EOG activity were amplified with a band-pass filter setting of 0.032 - 100 Hz; EMG was high-pass filtered at 5.2 Hz. Analog to digital conversion was performed at 256 Hz with 12 bit precision.

3.2.4. Data analysis

3.2.4.1. Motor response latency

For each subject, latencies of motor related activity following Go stimuli and latencies of erroneously executed motor activity following NoGo stimuli were determined. Motor response latency was defined as the time interval between onset of the imperative change in stimulus color and onset of motor response activity. Motor response onset was determined, off-line, by superimposing a vertical hairline cursor on the recorded EMG or EOG traces for finger and eye movement conditions, respectively (Barrett et al., 1985). Motor response latency was evaluated statistically by means of repeated measures analysis of variance (ANOVA). The analysis was performed with within-subject variables Go/NoGo (Go trials vs. NoGo trials), Movement Modality (finger extension vs. eye movement) and Movement Side (right vs. left finger extension, rightward vs. leftward eye movement).

3.2.4.2. Event related potentials (ERPs)

For each subject and movement condition, stimulus as well as response synchronized, averaged ERP profiles were constructed for Go and NoGo trials. Trials with artefacts in the ERPs, including eye movement artefacts, amplifier clipping and extensive EMG activity and/or electro-physiological drift, were rejected. Artefacts from required saccades in the eye movement conditions were corrected by means of a subtraction procedure described previously (see chapter 2). Averages subtended from 3.25 seconds preceding to one second following stimulus completion or movement onset. In the stimulus aligned epochs the first 250 ms, and in the response aligned epochs the first 70 ms of each epoch were used as pre-stimulus baseline. NoGo trials were defined either as 'correct' or 'incorrect'. Trials were designated 'correct' when either in the EMG trace for the finger extension conditions or in the horizontal EOG trace for the eye movement conditions, motor related activity was completely absent. When motor activity was evident, trials were defined as 'incorrect'. In the averaged ERP profiles for Go and 'incorrect' NoGo trials, trials were included when motor response latency was within one standard deviation of mean motor response latency on Go trials. For both movement modalities, mean motor response latency was obtained by averaging latency values of motor response activity on Go trials across subjects and across left and right side movement conditions. No latency limits were imposed for 'correct' NoGo trials.

Statistical analysis focused on ERP components following the imperative Go/NoGo stimulus, including positive component, P3, negative component, N2, and the 'error related negativity', N_e (Falkenstein et al., 1991). Components N2 and N_e were evident as negative deflections on the initial positive going limb of component P3, on 'correct' and 'incorrect' NoGo trials, respectively (see e.g., Fig. 4). For each subject, determination of latency values of ERP components, from the averaged cortical activity

recorded at electrode site Cz, was facilitated by superimposed vertical cursor hairlines. Component latencies were measured relative to imperative stimulus (S2) onset. ERP components analyzed were rather narrow. Therefore, component amplitudes were calculated by averaging ERP data samples also within a narrow time interval subtending 25 ms centred on peak latency (the latency at which maximum amplitude was recorded). Amplitude of component P3 was measured relative to maximum amplitude of the contingent negative variation (CNV) slow waveform (Grey Walter et al., 1964), recorded across the time interval between computer animation onset and imperative stimulus onset. As the CNV maximum was somewhat broader, CNV amplitude was calculated by averaging ERP data samples across a wider time inteval subtending 160 ms centred on peak CNV latency. The broader CNV time interval was selected to improve accuracy of the amplitude estimate. Amplitude values of components N2 and N_c were measured relative to mean ERP amplitude across a 25 ms interval centred on the latency at which a negative deflection appears on the positive going limb of component P3. Latency and amplitude values were evaluated statistically by means of repeated measures ANOVA. For component P3, analysis of latency values included within-subject variables Movement Modality (finger extension vs. eye movement) and variable Movement Side (right vs. left finger extension, rightward vs. leftward eye movement). In addition, variable Go/NoGo (Go trials vs. 'correct' NoGo trials) or variable Correct vs. Incorrect ('correct' NoGo trials vs. 'incorrect' NoGo trials) was included to compare latency values of ERP components between Go and 'correct' NoGo trials or between 'correct' and 'incorrect' NoGo trials. Variable Movement Side was omitted for analysis of ERPs averaged across right and left side movement conditions. Latency values of components N2 and N_c, for 'correct' and 'incorrect' NoGo trials, were evaluated in a single repeated measures design with within-subject variables N2 vs. N_c (N2 latency vs. N_c latency) and Movement Modality (finger extension vs. eye movement). For analysis of component amplitudes, similar statistical profiles were used. Within-subject variable Electrode (sites FCz, Cz, Pz and O'z) was added to evaluate midline amplitude topography. Bonferroni's correction method was applied to allow for multiple comparisons in the statistical analyses. When applicable, degrees of freedom were adjusted according to Geisser and Greenhouse (1958). In the present study, uncorrected degrees of freedom are reported to facilitate interpretation of the statistical design.

3.2.4.3. Error size

Motor actions on 'incorrect' NoGo trials were classified as either small or large errors. For finger extension, electro-myographic (EMG) activity was integrated (time constant: 0.05 s) over a 200 ms time interval starting at the onset of response related EMG activity. Actions were defined as small errors when EMG remained below 20% of the median integrated EMG activity for motor actions on Go trials. Motor responses were classified as large errors when response related EMG exceeded the 20% threshold. For eye movement, saccade amplitude was determined by calculating the average electro-oculographic (EOG) activity over a time interval subtending from saccade offset to 80 ms following saccade offset. Saccade amplitude was measured relative to the mean EOG activity across the first 500 ms preceding saccade onset. In general, saccadic

eye movements on NoGo trials ceased while close to the saccade target; only few saccades were substantially hypometric. As such, a higher percentage of EOG activity during eye movement Go trials was employed to classify saccades as small or large errors. When EOG amplitude on NoGo trials was below 85% of the median EOG deflection on Go trials, saccades were defined as small errors. Saccades with amplitude beyond the 85% limit were specified as large errors. Statistical analysis, by means of repeated measures ANOVA, was performed on the amplitude of component N_e for 'incorrect' NoGo trials with small errors and for 'incorrect' NoGo trials with large errors. To facilitate comparison, analysis also included the amplitude of component N2 on 'correct' NoGo trials with no errors. Within-subject variables included Movement Modality (finger extension vs. eye movement), Error Size (3 levels: 'correct' NoGo trials, 'incorrect' NoGo trials with small errors, 'incorrect' NoGo trials with large errors) and Electrode (midline electrode sites FCz, Cz and Pz).

In addition, averaged ERP profiles for 'correct' NoGo trials were subtracted from the cortical response profiles recorded for 'incorrect' NoGo trials with small and large errors. Mean size of the amplitude difference between 'correct and 'incorrect' NoGo trials was calculated across a 40 ms time interval centred on maximum amplitude of the difference waveform. Mean values were measured relative to the average amplitude across a 250 ms interval preceding onset of the amplitude difference. Calculated difference values were evaluated statistically by repeated measures ANOVA with within-subject variables Movement Modality (finger extension vs. eye movement), Error Size (large errors vs. small errors) and Electrode (FCz, Cz, Pz).

3.2.4.4. Stimulus versus response aligned averaging

To examine whether component N_e is time-locked more closely to imperative stimulus onset or to onset of motor response activity, stimulus aligned and motor response aligned cortical response profiles, averaged across 'incorrect' NoGo trials, were compared. Peak amplitude values of component N_e in the stimulus and response aligned waveforms at midline electrode sites FCz, Cz and Pz were examined by repeated measures ANOVA, with Alignment (stimulus vs. response synchronized averaging), Movement Modality (finger vs. eye movement) and Electrode as within-subject variables.

For additional analysis, separate averages were constructed for 'incorrect' NoGo trials with early and late onset of motor activity, respectively. It was hypothesized that if component N_e is time-locked more closely to the imperative stimulus, N_e onset and peak latency would be comparable across trials with early and late motor response onset in the stimulus aligned averages. Component N_e would occur earlier on trials with late onset of motor activity in the response locked averages. In contrast, if component N_e is time-locked more closely to motor response onset, the N_e would appear at a comparable latency in the response synchronized averages and would occur earlier on trials with early onset of motor activity in the stimulus synchronized averages. Motor response latency was classified as early or late when onset of motor activity either preceded or followed median motor response latency. For both movement modalities, median response latency was determined from the set of motor response latencies measured on 'incorrect' NoGo trials, across subjects and across right and left side movement

conditions. Statistical analysis of N_e latency values, by means of repeated measures ANOVA, was performed separately for stimulus and response synchronized averages. Within-subjects variables included Motor Response Latency (early vs. late motor response onset) and Movement Modality (finger vs. eye movement).

3.2.4.5. Lateralized readiness potential (LRP: see also chapter2 §2.2.4.3)

Motor related inter-hemispheric amplitude lateralization was assessed by means of the lateralized readiness potential (LRP) measure derived from stimulus synchronized ERPs (e.g., De Jong et al., 1988; Gratton et al., 1988). For statistical evaluation of inter-hemispheric amplitude differences in the LRP, three contiguous 100 ms time windows were defined across a time interval subtending from 100 ms following stimulus offset (t = 100 ms) to 400 ms following stimulus offset (t = 400 ms). Mean LRP values in each individual time window were calculated for every subject and were examined by means of Wilcoxon's test of paired differences. To account for multiple comparisons, significant inter-hemispheric asymmetry was assumed only when Wilcoxon's probability level was below p = 0.01.

3.3. Results

3.3.1. Motor response latency

Onset latencies for motor activity on Go trials and error responses on 'incorrect' NoGo trials, averaged across mean motor response latencies for each individual subject, are listed in Table 1. Mean motor response latency in the eye movement tasks was significantly longer than mean response latency in the finger extension tasks (variable Movement Modality; $F(1,9) = 52.41$, $p < 0.001$). Furthermore, for both movement modalities, reaction times were shorter on 'incorrect' NoGo trials compared with Go trials (variable Go/NoGo: $F(1,9) = 18.50$, $p = 0.002$; interaction Go/NoGo by Movement Modality: not significant). No significant differences were found for mean motor response latency of right compared with left finger extension or for mean response latency of rightward compared with leftward saccades.

	Right Finger Extension	Left Finger Extension	Saccades Rightward	Saccades Leftward
Go	179 ± 23	167 ± 29	211 ± 22	209 ± 25
incorrect NoGo	147 ± 20	139 ± 28	194 ± 36	192 ± 38

Table 1: *Mean motor response latencies (± standard error of the mean) on Go and 'incorrect' NoGo trials for each movement condition. Latency data for motor activity on Go trials have been adapted from chapter 2.*

3.3.2. Event related potentials

For Go and 'incorrect' NoGo averages, trials were included when motor

response latency was within 170.8 ms ± 60.0 (latency range: 110.8 - 230.8 ms) for finger movement and within 209.9 ms ± 60.2 (latency range: 149.7 - 270.1 ms) for saccadic eye movement (latency intervals are derived from chapter 2). For each subject and movement condition, on average 40 Go and 40 NoGo trials were selected. About 30% of the NoGo trials were labeled 'incorrect'.

3.3.2.1. Go trials / 'correct' NoGo trials

Stimulus aligned ERPs, averaged across subjects, on Go trials (bold traces) and 'correct' NoGo trials (thin lined traces) are depicted in Fig. 2 and Fig. 3. ERP components discernible in the cortical activity recorded during performance of the experimental task are illustrated in Fig. 4. Response profiles recorded at electrode site FCz, averaged across subjects and across right and left side movement conditions, are depicted. Waveforms consist of an early positive ERP component, P1, and negativity, N2, elicited by computer animation onset (S1), followed by a relatively broad positivity, P3, peaking at about 240 ms following S1. Subsequently, the contingent negative variation (CNV) develops, composed of an initial CNV (iCNV) and a late or terminal CNV (tCNV) (Weerts and Lang, 1973). The CNV is followed by a positive component at approximately 40 ms preceding the imperative stimulus (S2). This final positivity, labeled P3, peaks at about 325 ms following S2. In addition, on 'correct' NoGo trials for both movement modalities, a small negative deflection, labeled N2, appears at a latency of about 250 ms relative to S2 (Fig. 4). Component P3 as well as component N2, superimposed on the initial positive going limb of component P3, are most pronounced at frontal-central electrode sites. For more detailed description of ERP components, see chapter 2. Data analysis in the present study concentrates exclusively on ERP components recorded following S2.

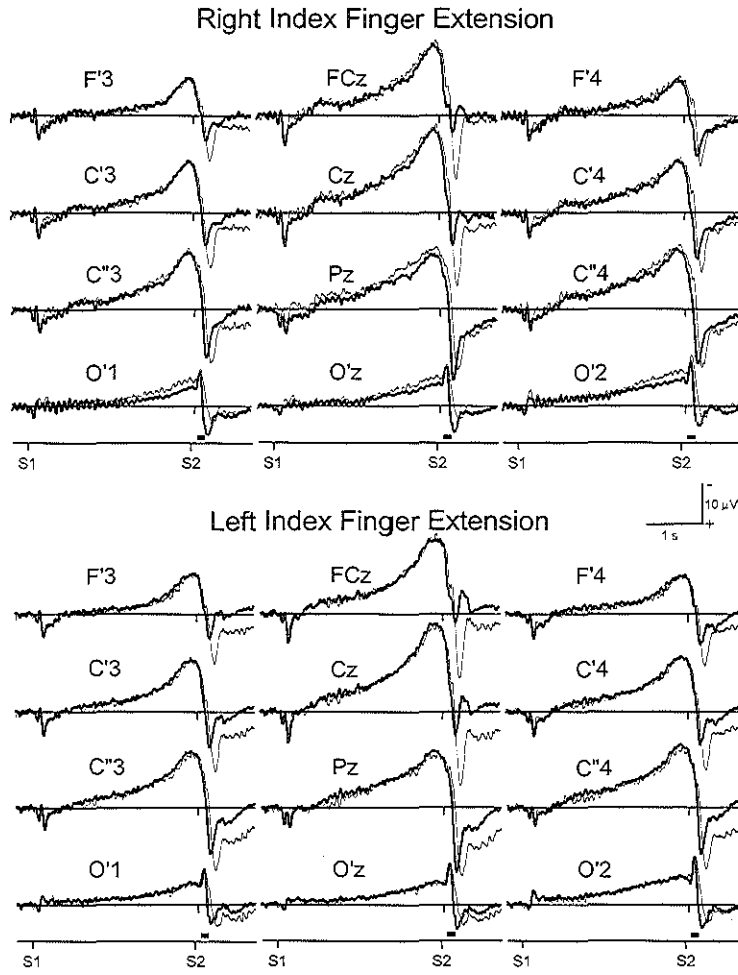


Figure 2: *Stimulus synchronized ERPs on Go trials (bold traces) and 'correct' NoGo trials (thin traces), for finger movement conditions. Upper panel: right index finger extension; lower panel: left index finger extension. Traces are depicted in order of the employed electrode montage. Computer animation onset (S1) and imperative color change onset (S2) are indicated below the occipital traces. Range of movement onset for motor responses on Go trials is illustrated by the small solid horizontal bars. An enhancement of component P3, following the imperative stimulus, is evident on 'correct' NoGo trials compared with Go trials, especially at frontal (F'3, FCz, F'4) and central (C'3, Cz, C'4, C"3, C"4) electrode sites. In addition, for 'correct' NoGo trials following S2, a small negative deflection is evident on the initial positive-going limb of component P3. This negative component, labeled N2, also is most pronounced at frontal-central scalp sites. The averaged ERPs on Go trials are derived from chapter 2.*

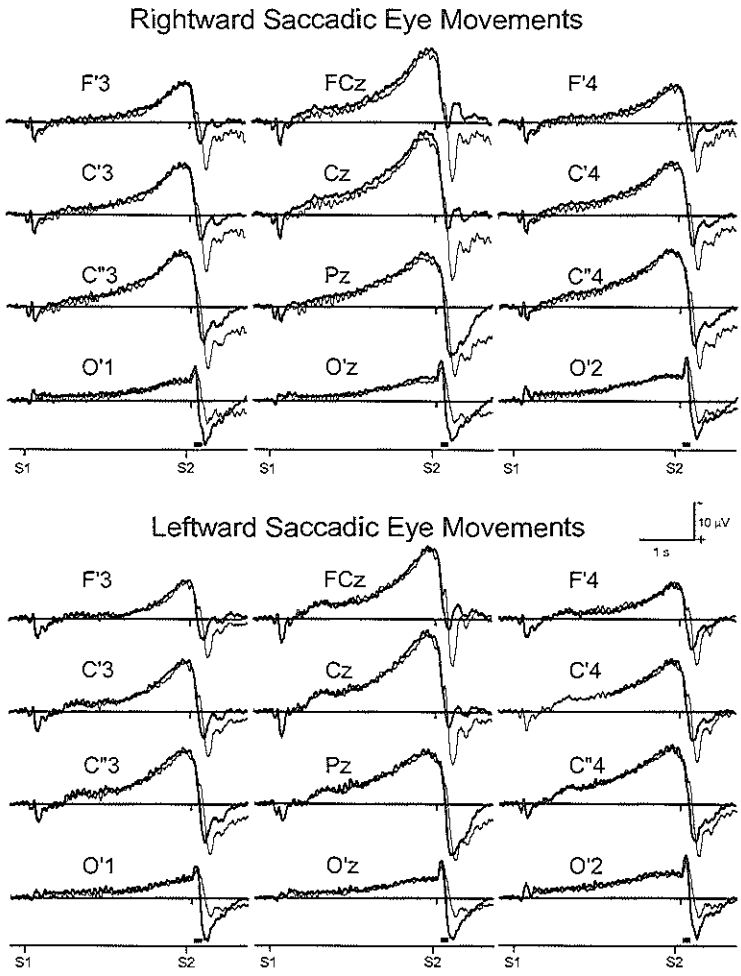


Figure 3: *Stimulus synchronized ERPs on Go trials (bold traces) and 'correct' NoGo trials (thin traces) for eye movement conditions. Upper panel: rightward saccadic eye movement; lower panel: leftward saccadic eye movement. See also figure legend 2 for more detail. As with finger movement (Fig. 2), component P3 following the imperative stimulus (S2) is enhanced on 'correct' NoGo trials compared with Go trials, particularly at frontal-central electrode sites. On 'correct' NoGo trials, a negative deflection N2 on the descending limb of component P3 also is evident. Averaged cortical activity across Go trials are derived from chapter 2.*

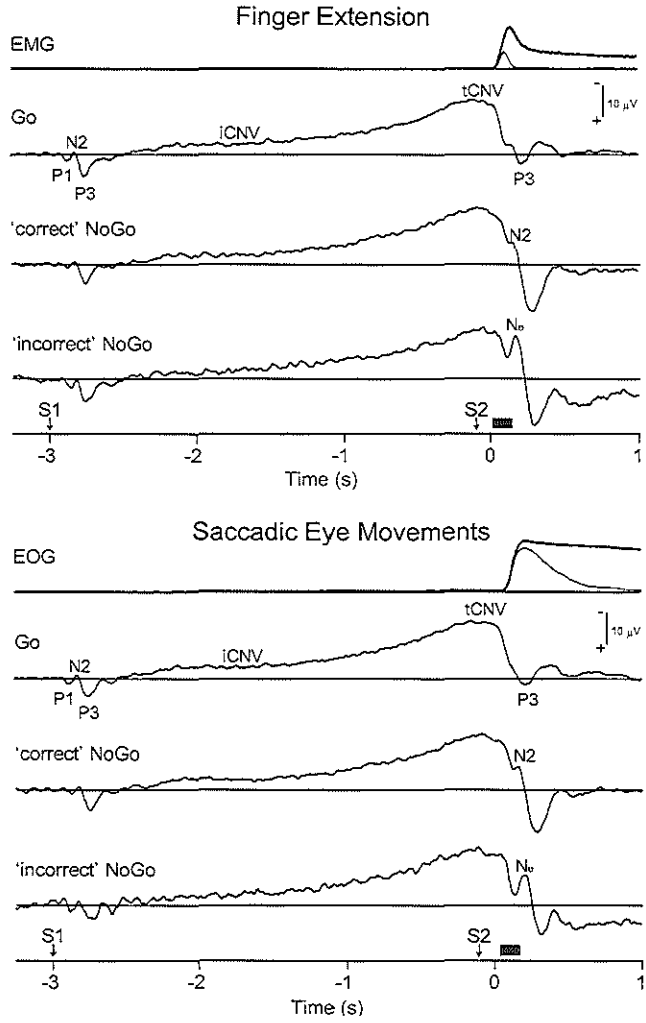


Figure 4: *Cortical activity, recorded at electrode site FCz, on Go trials and 'correct' and 'incorrect' NoGo trials for finger extension (upper panel) and saccadic eye movement (lower panel) conditions. Identified ERP components in the cortical activity recorded during task performance are illustrated. EMG and EOG traces depict motor response activity for finger extension and saccadic eye movement, respectively. Bold traces for the EMG or EOG (upper traces) represent motor related activity recorded on Go trials; remaining thin lined traces depict motor activity on 'incorrect' NoGo trials. Motor activity is absent during 'correct' NoGo trials. Computer animation onset (S1) and imperative stimulus onset (S2) are indicated above the time axes. Solid horizontal bars represent onset range of motor activity.*

Go trials / 'correct' NoGo trials

P3

Right Finger Extension = Left Finger Extension

Peak amp.	Go	< corr. NoGo	Go	< corr. NoGo
FCz	21.9 ± 4.7	33.5 ± 13.3	21.7 ± 5.0	35.9 ± 10.8
Cz	28.6 ± 5.6	39.3 ± 11.5	28.2 ± 6.8	40.2 ± 8.7
Pz	30.8 ± 5.3	30.0 ± 6.9	29.7 ± 5.8	29.8 ± 4.4
O'z	11.9 ± 3.4	9.9 ± 2.6	11.6 ± 3.7	9.6 ± 2.6
Peak lat.	312 ± 18	369 ± 27	312 ± 29	382 ± 40

P3

Rightward Saccades = Leftward Saccades

Peak amp.	Go	< corr. NoGo	Go	< corr. NoGo
FCz	21.6 ± 9.1	34.2 ± 12.5	23.0 ± 10.5	32.0 ± 11.1
Cz	26.2 ± 7.0	38.5 ± 10.8	26.0 ± 9.7	35.1 ± 8.6
Pz	25.8 ± 5.1	30.1 ± 4.7	26.8 ± 5.8	27.0 ± 4.7
O'z	13.9 ± 5.8	10.5 ± 3.0	14.5 ± 3.5	9.3 ± 3.7
Peak lat.	311 ± 25	404 ± 36	319 ± 39	387 ± 34

'correct' NoGo trials / 'incorrect' NoGo trials

$N2/N_e$

	Finger Extension		Saccades	
Peak amp.	N2	N_e	N2	N_e
FCz	2.2 ± 3.1	9.6 ± 4.3	2.6 ± 2.9	8.6 ± 5.9
Cz	1.9 ± 2.7	8.8 ± 4.7	2.0 ± 2.8	8.3 ± 5.4
Pz	0.7 ± 2.3	1.1 ± 3.1	0.0 ± 2.0	2.8 ± 4.0
Onset lat.	212 ± 31	210 ± 12	232 ± 15	245 ± 22
Peak lat.	236 ± 33	262 ± 19	258 ± 21	305 ± 29

P3

	Finger Extension		Saccades	
Peak amp.	corr. NoGo	incorr. NoGo	corr. NoGo	incorr. NoGo
FCz	34.7 ± 11.8	32.9 ± 10.3	33.1 ± 11.0	31.0 ± 10.8
Cz	40.0 ± 9.9	35.6 ± 9.4	36.4 ± 8.8	33.2 ± 8.9
Pz	29.8 ± 5.5	27.9 ± 5.6	27.8 ± 3.5	29.4 ± 3.3
O'z	9.8 ± 2.4	9.9 ± 3.0	9.5 ± 3.3	15.8 ± 3.0
Peak lat.	370 ± 21	392 ± 24	392 ± 35	421 ± 34

Table 2: *Left panel: peak amplitude, at midline electrode sites FCz, Cz, Pz and O'z, and peak latency (row labeled peak lat.) of component P3, for each movement condition, on Go trials (column labeled 'Go') and 'correct' NoGo trials (column labeled 'corr. NoGo'). Right upper panel: peak amplitude, for midline sites FCz, Cz and Pz, and onset and peak latencies of components N2 and N_e on 'correct' and 'incorrect' NoGo trials. Amplitude and latency values are derived from ERPs averaged across right and left finger extension conditions and across right- and leftward saccadic eye movement conditions. Right lower panel: peak amplitude and latency values of component P3 on 'correct' and 'incorrect' NoGo trials, determined from ERPs averaged across right and left side movement conditions.*

Component P3: Amplitude values of component P3 on Go trials (symbols connected by solid lines) and 'correct' NoGo trials (symbols connected by dashed lines), for each movement condition, are depicted in the top left and right panels of Fig. 5. Corresponding amplitude data also are listed, with standard deviations, in the left panel of Table 2. Statistical analysis showed that the amplitude of component P3 was enhanced on 'correct' NoGo trials compared with Go trials (variable Go/NoGo: $F(1,9) = 12.04$, $p = 0.014$). A significant Go/NoGo by Electrode interaction ($F(3,27) = 39.30$, $p < 0.001$) indicated that the increase in P3 amplitude was observed primarily at frontal-central electrode sites, FCz and Cz. Interactions Go/NoGo by Movement Modality and Go/NoGo by Movement Side were non-significant. Further, no inter- or intra-modality differences in P3 amplitude were found, neither between finger extension and saccadic eye movement, between right and left finger extension or between right- and leftward saccades (variables Movement modality, Movement Side and their interaction: non-significant). A significant Go/NoGo by Movement Modality by Movement Side interaction was found ($F(1,9) = 7.51$, $p = 0.046$). The latter interaction is explained by the fact that on 'correct' NoGo trials for eye movement, component P3 is slightly enhanced on rightward compared with leftward saccades (Fig.5: top right panel).

Peak latency values of component P3 also are listed in the left panel of Table 2. P3 latency was prolonged on 'correct' NoGo trials compared with Go trials (variable Go/NoGo: $F(1,9) = 224.85$, $p < 0.001$). A significant main effect for variable Movement Modality ($F(1,9) = 13.08$, $p = 0.012$) also indicated that P3 latency was longer for eye movement compared with finger movement. The interaction Go/NoGo by Movement Modality was not significant. P3 latency was comparable for right and left finger extension as well as for right- and leftward saccades (variable Movement Side and interactions with variable Movement Side: not significant).

3.3.2.2. 'Correct'/ 'incorrect' NoGo trials

As the number of 'incorrect' NoGo trials was relatively small, for subsequent analysis, ERPs were averaged across right and left side movement conditions. Averaged cortical activity, recorded at scalp site FCz, on 'incorrect' NoGo trials also is depicted in Fig. 4. For finger extension as well as saccadic eye movement, a negative component, labeled N_e, is evident at a similar latency as observed for component N2 on 'correct' NoGo trials. Scalp distributions of components N_e and N2 also appeared comparable.

Components N2 / N_e: Peak amplitude values of component N2 on 'correct' NoGo trials and component N_e on 'incorrect' NoGo trials are depicted in Fig. 5 (middle left and right panels) and in the upper right of Table 2. Amplitude data are displayed for midline electrode sites FCz, Cz and Pz; components N2 and N_e could not be identified at occipital sites. In the statistical analysis, a significant main effect for variable Electrode was found ($F(2,18) = 27.64$, $p < 0.001$). Analysis by means of univariate F-tests indicated that N2 and N_e amplitude values were enhanced at frontal-central electrode sites FCz and Cz compared with parietal site Pz (FCz/Cz vs. Pz: $F(1,9) = 31.02$, $p < 0.001$). Peak amplitudes at electrode sites FCz and Cz were not significantly different. Amplitude of component N_e was enhanced compared with N2 amplitude (variable N2 vs. N_e: $F(1,9) = 26.01$, $p = 0.001$), primarily at frontal-central electrode

sites (N2 vs. N_c by Electrode interaction: $F(2,18) = 29.69$, $p < 0.001$). N2 and N_c amplitude values as well as the enhancement of N_c amplitude compared with N2 amplitude were similar for finger extension and eye movement (variable Movement Modality and interaction N2 vs. N_c by Movement Modality: not significant).

Onset and peak latency values of components N2 and N_c also are summarized in the top right panel of Table 2. Onset and peak latency of components N2 and N_c were prolonged for eye movement compared with finger movement (variable Movement Modality: onset latency: $F(1,9) = 11.70$, $p = 0.008$; peak latency: $F(1,9) = 8.83$, $p = 0.016$). Interactions N2 vs. N_c by Movement Modality were not significant. N_c peak latency was prolonged compared with N2 peak latency (variable N2 vs. N_c: $F(1,9) = 42.65$, $p < 0.001$). Further, a significant difference between onset latencies of components N2 and N_c was not found.

Component P3: Bottom panels of Fig. 5 and lower right of Table 2 depict, for midline electrode sites, peak amplitude values of component P3 on 'correct' and 'incorrect' NoGo trials. In the statistical analysis, a Correct vs. Incorrect by Electrode interaction ($F(3,27) = 13.14$, $p = 0.002$) revealed that P3 amplitude at frontal-central electrode sites (FCz, Cz) was enhanced on 'correct' NoGo trials compared with 'incorrect' NoGo trials. A significant Movement Modality by Electrode interaction ($F(3,27) = 6.69$, $p = 0.038$) indicated, in addition, that at frontal-central electrode sites P3 amplitude tended to be larger with finger extension. Main variables Movement Modality and Correct vs. Incorrect and interaction Correct vs. Incorrect by Movement Modality were not significant.

In the bottom right panel of Table 2, peak latency values of component P3 on 'correct' and 'incorrect' NoGo trials are listed. P3 latency was prolonged for saccadic eye movement compared with finger extension (variable Movement Modality: $F(1,9) = 16.04$, $p = 0.006$). A significant main effect for variable Correct vs. Incorrect ($F(1,9) = 40.03$, $p < 0.001$) indicated that P3 latency was enhanced on 'incorrect' NoGo trials compared with 'correct' NoGo trials. The interaction Correct vs. Incorrect by Movement Modality was not significant.

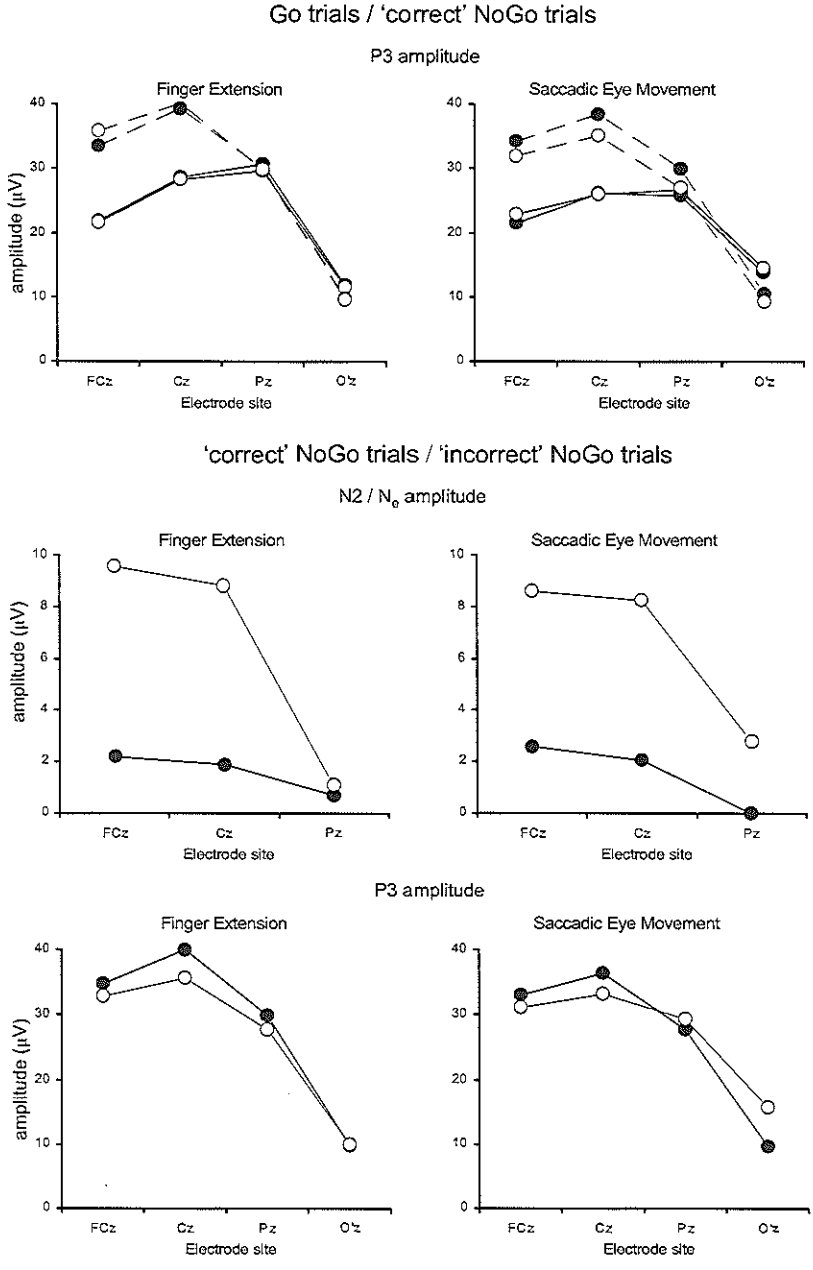

Go trials / 'correct' NoGo trials
P3 amplitude
Finger Extension
Saccadic Eye Movement
amplitude (µV)
40
30
20
10
0
FCz
Cz
Pz
O'z
Electrode site
'correct' NoGo trials / 'incorrect' NoGo trials
N2 / Ne amplitude
Finger Extension
Saccadic Eye Movement
amplitude (µV)
10
8
6
4
2
0
FCz
Cz
Pz
Electrode site
P3 amplitude
Finger Extension
Saccadic Eye Movement
amplitude (µV)
40
30
20
10
0
FCz
Cz
Pz
O'z
Electrode site

Figure 5: *Peak amplitude values, at midline electrode sites FCz, Cz, Pz and O'z, of ERP components P3 and N2 / N_c, following the imperative Go/NoGo stimulus (S2). Left panels depict finger movement, right panels depict eye movement. Amplitude values also are listed, with standard deviations, in Table 2. Top panels of figure 5 depict peak amplitude of component P3 on Go trials (continuous lines) and 'correct' NoGo trials (dashed lines), for each individual movement condition. Filled and open symbols represent right and left side movement conditions, respectively. Amplitude of component P3, at scalp sites FCz and Cz, is enhanced on 'correct' NoGo trials compared with Go trials. The enhancement of P3 amplitude is observed for both movement modalities. Middle and bottom panels depict peak amplitude of components N2 / N_c and P3 on 'correct' and 'incorrect' NoGo trials, determined from ERPs averaged across right and left side movement conditions. For both movement modalities, N_c amplitude on 'incorrect' NoGo trials (middle panels; open circles) is enhanced compared with N2 amplitude on 'correct' NoGo trials (middle panels; filled circles), at frontal-central electrode sites FCz and Cz. Amplitude of positivity P3 (bottom panels) is enhanced on 'correct' NoGo trials (filled symbols) compared with 'incorrect' NoGo trials (open symbols), also primarily at scalp sites FCz and Cz.*

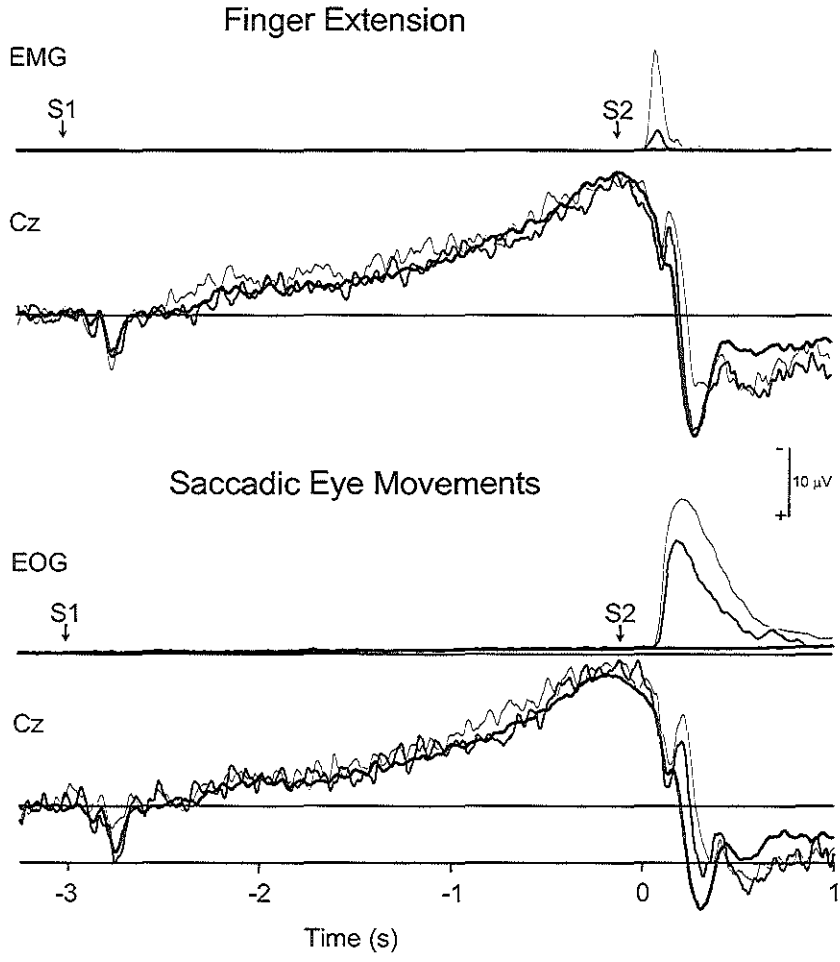


Figure 6: *Cortical response profiles, recorded at electrode site Cz, on 'correct' NoGo trials (bold traces), 'incorrect' NoGo trials with small errors (intermediate bold traces) and 'incorrect' NoGo trials with large errors (thin traces), during finger movement (upper traces) and eye movement (lower traces) conditions. EMG and EOG traces depict accompanying motor response activity for finger and eye movement, respectively. Computer animation onset and imperative stimulus onset are labeled S1 and S2.*

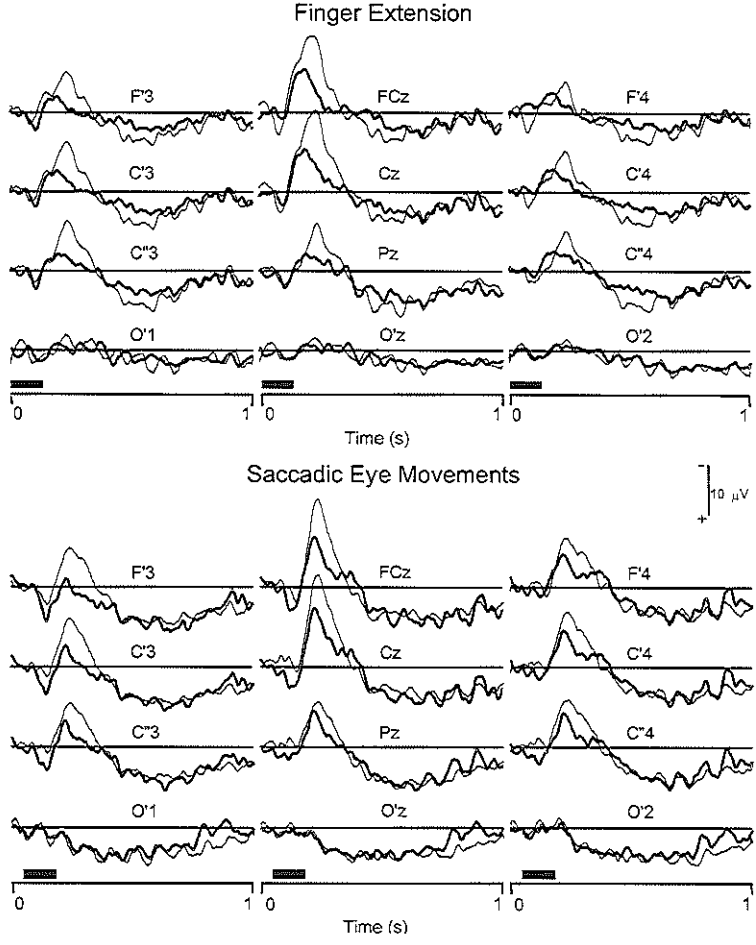


Figure 7: *Difference waveforms, for finger extension (upper panel) and eye movement (lower panel), obtained by subtracting ERP profiles, averaged across subjects, on 'correct' NoGo trials from ERPs recorded on 'incorrect' NoGo trials with small errors (bold traces) and 'incorrect' NoGo trials with large errors (thin traces). Difference waveforms, at each electrode site, are depicted within a time window subtending from stimulus completion (t = 0 s) to 1 s following stimulus completion (t = 1 s). Horizontal bars above the time axes represent range of motor response onset. Component N_e on 'incorrect' NoGo trials is evident as a well-defined negative displacement in the difference waveforms. The amplitude difference is largest at frontal-central electrode sites (F'3, FCz, F'4, C'3, Cz, C'4, C"3, C"4). In addition, difference waveforms for both movement modalities indicate that component N_e is most pronounced on NoGo trials with large errors.*

3.3.3. Error size

Fig. 6 depicts cortical response profiles recorded at electrode site Cz, averaged across subjects and across right and left side movement conditions, on 'correct' NoGo trials (bold traces), 'incorrect' NoGo trials with small errors (traces with intermediate thickness) and 'incorrect' NoGo trials with large errors (thin lined traces). Motor response activity recorded for finger and eye movement is depicted by means of EMG and EOG traces, respectively. With finger extension, for each subject on average 15 'incorrect' NoGo trials with small errors and 13 'incorrect' NoGo trials with large errors were obtained. For eye movement, average numbers per subject were 9 NoGo trials with small errors and 14 NoGo trials with large errors. In the statistical analysis, N_e amplitude was comparable for finger extension and saccadic eye movement (variable Movement Modality: not significant). A main effect for variable Error size was found ($F(2,18) = 11.07$, $p = 0.001$). Analysis by means of univariate F-tests indicated that amplitude of component N_e on 'incorrect' NoGo trials was enhanced compared with N2 amplitude on 'correct' NoGo trials ($F(1,9) = 21.3$, $p = 0.001$). A significant difference between N_e amplitude for 'incorrect' NoGo trials with small or large errors was absent.

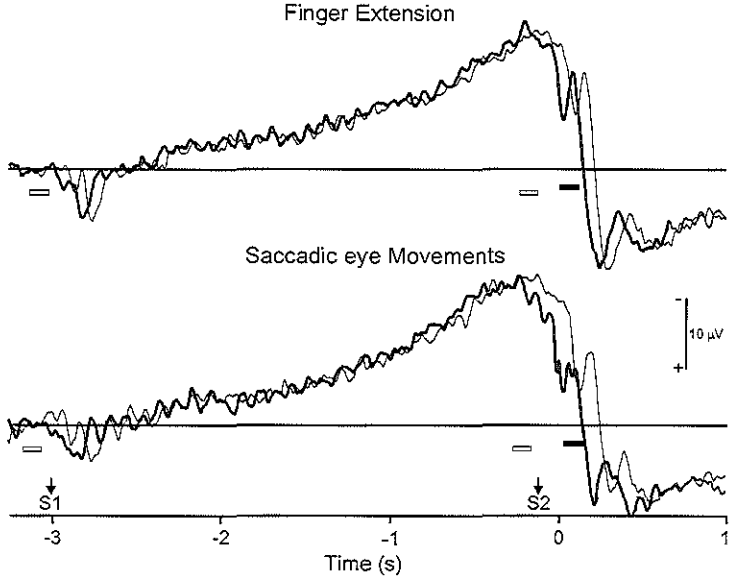
Difference waveforms obtained by subtracting averaged ERP profiles on 'correct' NoGo trials from the ERP profiles obtained on 'incorrect' NoGo trials are depicted in Fig. 7, for NoGo trials with small errors (bold traces) and NoGo trials with large errors (thin lined traces). Waveforms are displayed within a time interval subtending from computer animation offset ($t = 0$ s) to 1 s following computer animation offset ($t = 1$ s). In the difference waveforms, for finger extension as well as saccadic eye movement, component N_e on 'incorrect' NoGo trials is evident as a well-defined negative displacement. In the statistical analysis, amplitude of the negative displacement was comparable for finger extension and eye movement (variable Movement modality and interactions including variable Movement modality: not significant). A main effect for variable Electrode ($F(2,18) = 16.80$, $p = 0.001$) was found. Analysis by means of univariate F-tests indicated that the enhanced negativity in the N_e latency range was most pronounced at frontal-central electrode sites (FCz, Cz vs. Pz: $F(1,9) = 22.58$, $p = 0.001$). The amplitude difference was largest on NoGo trials with large errors (variable Error Size: $F(1,9) = 39.25$, $p < 0.001$).

3.3.4. Stimulus versus response synchronized averaging

Upper traces of Fig. 8 show stimulus synchronized ERPs (thin lined traces) as well as response synchronized ERPs (bold traces), recorded at electrode site Cz, averaged across subjects and across right and left side movement conditions. For finger extension, both amplitude and waveform of component N_e are comparable with stimulus and response locked averaging. With eye movement, component N_e appears somewhat more smeared in the response synchronized profile; the waveform appears double-peaked. In the statistical analysis, no significant differences in amplitude of component N_e were found, neither between stimulus and response triggered averages nor between finger extension and eye movement.

For subsequent analysis, onset and peak latency of component N_e were evaluated for 'incorrect' NoGo trials with onset of motor response activity either preceding or following median motor response latency. Median motor response latency

on 'incorrect' NoGo trials was 166 ms for finger extension and 205 ms for eye movement. With finger extension, for each subject on average 14 NoGo trials with early and 14 NoGo trials with late onset of motor activity were obtained. With eye movement, on average 12 trials per subject were obtained for each latency category. Lower traces of Fig. 8 show stimulus triggered averages (left) and response triggered averages (right) of 'incorrect' NoGo trials with early (thin traces) and late (thick traces) motor response onset. Onset and peak latency values of component N_c for each condition are listed in Table 3. With stimulus synchronized averaging, N_c onset latency was prolonged on 'incorrect' NoGo trials with late motor response onset (variable Motor Response Latency: $F(1,9) = 6.09$, $p = 0.036$). No significant difference was found for N_c peak latency. With response synchronized averaging, both N_c onset and peak latency were prolonged on trials with early motor response onset (variable Motor Response Latency; onset latency: $F(1,9) = 16.78$, $p = 0.003$, peak latency: $F(1,9) = 17.18$, $p = 0.003$).



Stimulus Synchronized Averaging

Response Synchronized Averaging

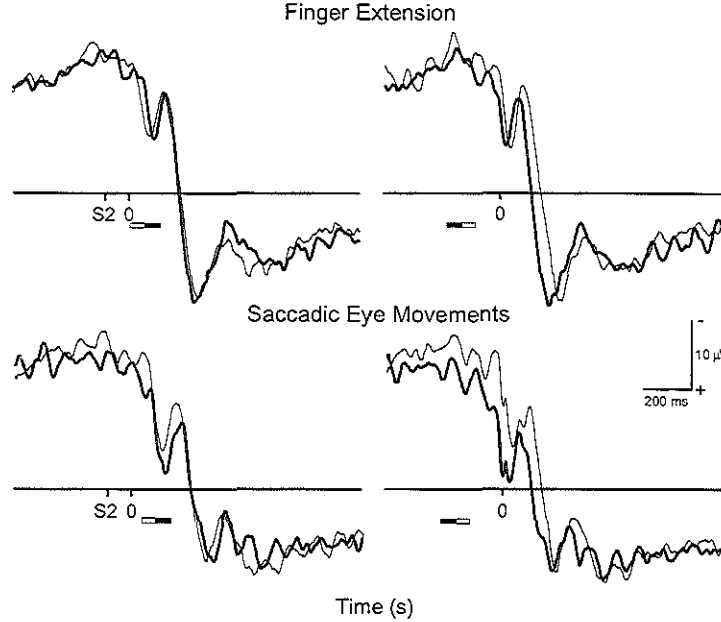


Figure 8: *Stimulus and response locked cortical response profiles for 'incorrect' NoGo trials. Top panels: stimulus locked averages (thin lined traces) and response locked averages (bold traces) during finger movement and saccadic eye movement conditions. With stimulus synchronized averaging, offset of the computer generated animation is at t = 0 s; filled horizontal bars illustrate range of motor response onset. Stimulus onset (S1) and onset of the imperative color change (S2) are indicated above the time axis. With response synchronized averaging, t = 0 s represents motor response onset; open horizontal bars depict the range of computer animation onset (S1) and imperative stimulus (S2) onset. Bottom panels: ERPs recorded at scalp site Cz for 'incorrect' NoGo trials with early (thin lined traces) and late (bold traces) motor response onset. Cortical response profiles for both movement modalities are depicted in a time window subtending from 500 ms preceding to 1 s following stimulus completion or motor response onset. With stimulus synchronized averaging (left), completion of the computer generated animation is at t = 0 s; imperative stimulus onset (S2) is at t = -100 ms. With response synchronized averaging (right), t = 0 s represents motor response onset. Horizontal bars below the time axes indicate range of motor response onset, with stimulus aligned averaging, or range of imperative stimulus onset, with response aligned averaging. Open and filled sections illustrate onset range for trials with early onset and late onset of motor response activity, respectively.*

	Stimulus synchronized averaging			
	Finger Extension		Saccades	
	Early	Late	Early	Late
Onset	203 ± 20	216 ± 21	240 ± 14	251 ± 24
Peak	253 ± 20	264 ± 22	306 ± 22	307 ± 31
	Response synchronized averaging			
	Finger Extension		Saccades	
	Early	Late	Early	Late
Onset	48 ± 19	30 ± 22	54 ± 16	37 ± 21
Peak	99 ± 19	83 ± 21	119 ± 24	89 ± 27

Table 3: *Onset and peak latency values of component N_e on 'incorrect' NoGo trials with early onset (column labeled 'Early') and late onset (column labeled 'Late') of motor activity. Latency values are determined from stimulus synchronized (upper panel) as well as motor response synchronized (lower panel) averaged cortical activity. Component latencies are measured either relative to imperative stimulus (S2) onset, with stimulus locked averaging, or with respect to motor response onset, with response synchronized averaging.*

3.3.5. Lateralized readiness potential (LRP)

Fig. 9 shows LRP profiles for finger extension and saccadic eye movements, within a time window subtending from one second prior to completion of the computer animation (t = −1 s) to one second following computer animation offset (t = 1 s). LRP waveforms depicted are obtained from electrode pairs C' (C'3 vs. C'4) and C" (C"3 vs. C"4) across central cortical areas. For finger extension, on Go trials (thin traces) a preponderance of cortical negativity across the hemisphere contralateral to the movement side (upward deflection) is evident during movement execution. Significant inter-hemispheric lateralization was found in the LRP for electrode pair C', within a time interval subtending from 200 ms to 300 ms following the imperative stimulus, and in the LRP derived from pair C", during a time interval subtending from 100 ms to 200 ms following S2. Comparable lateralization is evident on 'incorrect' NoGo trials (traces with intermediate thickness). For the latter, however, inter-hemispheric asymmetry is less pronounced and resolves earlier. Significant inter-hemispheric lateralization was found only in the LRP derived from electrode pair C", during a time interval subtending from 100 ms to 200 ms following S2. On 'correct' NoGo trials (bold traces), a tendency toward contralateral cortical response dominance, albeit not statistically significant, also was noted.

With eye movement, a preponderance of cortical response negativity over the hemisphere contralateral to saccade direction was not detected at any electrode pair, neither on Go trials (see also § 2.3.3 of chapter 2) nor on 'correct' or 'incorrect' NoGo trials. Significant inter-hemispheric lateralizations also were absent.

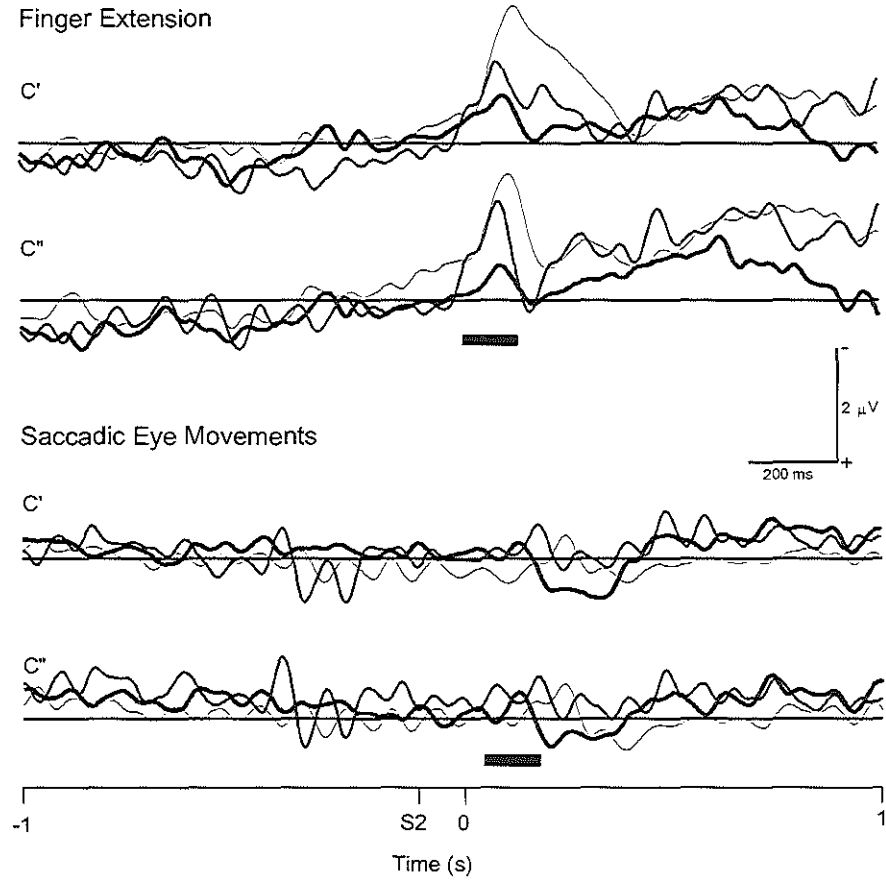


Figure 9: *LRP profiles for electrode pairs C' (C'3 vs. C'4) and C" (C"3 vs. C"4), derived from stimulus synchronized ERPs, for finger extension (upper traces) and saccadic eye movements (lower traces). Onset of the imperative color change (S2) is indicated on the time axis. Negative values of the LRP profiles (plotted upward) indicate a preponderance of cortical negativity over the hemisphere contralateral to the side of the movement. Thin lined traces represent LRPs derived for Go trials; thick traces represent LRPs on 'correct' NoGo trials. Traces with intermediate thickness depict LRPs on 'incorrect' NoGo trials. The horizontal bar below the LRP profiles in each panel represents the onset range of motor activity on Go and 'incorrect' NoGo trials.*

3.4. Discussion

Event related potentials were evaluated in a Go/NoGo reaction time task performed with four movement conditions; right index finger extension, left index finger extension, rightward saccadic eye movement and leftward saccadic eye movement. A visual pacing stimulus provided exact information on the time at which an imperative Go/NoGo signal occurred. During presentation of the pacing stimulus, contingent negative variation (CNV) slow wave cortical activity was recorded. Following the imperative Go/NoGo signal, the CNV was terminated by a late positivity, labeled P3. On 'correct' NoGo trials, a negative component, labeled N2, was evident and superimposed on the positive going limb of component P3. On 'incorrect' NoGo trials an error negativity (N_e) was observed at a latency comparable to component N2. Morphology, amplitude and scalp topography of components P3, N2 and N_e were comparable for finger and eye movement conditions. Component latencies were prolonged with eye movement. Analysis of N_e amplitude as a function of error size suggested that component N_e is progressively enhanced on 'incorrect' NoGo trials with larger errors committed. Comparison of stimulus and response synchronized averaged ERPs indicated that component N_e is not perfectly time-locked either to motor response onset or to the onset of the imperative Go/NoGo stimulus. Finally, on Go trials with finger movement, a preponderance of cortical activity over the hemisphere contralateral to the movement side was evident in the lateralized readiness potential (LRP), across central cortical areas. On NoGo trials, an initial development of contralateral lateralization was present which appeared interrupted. A correlate of the LRP detected during finger movement was absent during saccadic eye movement.

3.4.1. Motor response latency

Mean motor response latency was significantly shorter for motor activity on 'incorrect' NoGo trials compared with motor activity on Go trials. This observed latency difference is in agreement with the Race model (Logan and Cowan, 1984; Osman et al., 1986), which proposes that on NoGo trials, in a Go/NoGo reaction time paradigm, only those motor responses survive which are initiated early enough to outrun inhibitory mechanisms. In addition, in the present study, mean motor response latency was prolonged for eye movement compared with finger movement. However, this reaction time difference may have resulted primarily from the different measures of response onset used for both movement modalities. That is, with finger movement, motor response onset was defined as the onset of response related muscle activity, while with eye movement, response onset was specified as the onset of the saccade (see also chapter 2). No significant differences were found when motor response latency was compared for right and left side movement conditions.

3.4.2. Event related potentials

The P3 and N2 Go/NoGo differences observed in the present study replicate results of earlier studies (Karlin et al., 1970; Hillyard et al., 1976; Simson et al., 1977; Pfefferbaum et al., 1985; Pfefferbaum and Ford., 1988; Kok, 1986; Jodo and Inou, 1990; Roberts et al., 1994). The enhancement of negativity N2, at a latency of about

200-400 ms following NoGo stimuli, has been related to cortical function associated with suppression of intended movement (Pfefferbaum et al., 1985; Kok, 1986; Eimer, 1993; Jodo and Kayama, 1992). Response inhibition processing similarly has been proposed for the frontal-central enhancement of component 'P300' (Karlin et al., 1970; Roberts et al., 1994). Previous studies also purport that the 'P300' following Go stimuli is either distinct from the 'P300' following NoGo stimuli (Pfefferbaum and Ford, 1988; Jodo and Inoue, 1990; Jodo and Kayama, 1992; Eimer, 1993), or that two 'P300' generators are present, with different overlap on Go and NoGo trials (Falkenstein et al., 1995). Alternatively, several studies have proposed that 'P300' amplitude may be reduced on Go trials due to overlap with motor related cortical negativity which is present following Go stimuli but is withheld following NoGo stimuli (Simson et al., 1977; Kok, 1986; Kok, 1988; Kopp et al., 1996b).

In the present study, during 'incorrect' NoGo trials, a negative component, labeled 'error negativity' (N_e), appeared at a comparable latency observed for component N2 on 'correct' NoGo trials. N_e amplitude was larger than N2 amplitude primarily at frontal-central electrode sites. As described in previous studies, component N_e has been related to cortical function associated with error-detection processing (e.g., Falkenstein et al., 1995; Scheffers et al., 1996) Moreover, in a recent study, Holroyd et al. (1998) demonstrated that the N_e is comparable with suppression of either intended hand or foot movement. Accordingly, Holroyd and colleagues suggested that component N_e reflects an output-independent error-processing function. The present finding of a similar error negativity (N_e) with either finger movement or saccadic eye movement also indicates that the N_e can be generalized across movement modalities. In addition, comparable N2 and P3 Go/NoGo differences for either movement modality suggests that cortical mechanisms underlying the observed Go/NoGo effects on ERP components N2 and P3 also are output independent.

3.4.3. Error size

In the averaged ERP profiles for finger extension and saccadic eye movement, N_e amplitude was comparable for 'incorrect' NoGo trials with small and large errors. This result is in agreement with Scheffers et al. (1996) who observed no relationship between N_e amplitude and force of inappropriately initiated motor actions. However, in contrast to the analysis of N_e amplitude from the averaged ERP profiles, analysis of difference waveforms in the present study, obtained by subtracting averaged ERPs recorded on 'correct' NoGo trials from ERP profiles on 'incorrect' NoGo trials, suggests that component N_e is enhanced on NoGo trials with large errors. These contradictory findings may be explained by temporal overlap of components N_e and P3. That is, complete development of the N_e in the averaged ERP profiles may well have been concealed by the onset of subsequent positivity, P3. In the present study, amplitude of component P3 was significantly reduced on 'incorrect' NoGo trials compared with 'correct' NoGo trials. Falkenstein et al. (1991) also observed a reduction in 'P300' amplitude for error NoGo trials and proposed that the amplitude decrease was due to overlap with an error related negativity. Component overlap is overcome via difference waveforms which take into account the initial development of the error processing negativity, evident in the original unsubtracted waveforms, as well as the subsequent

reduction of P3 amplitude. However, it should be noted that the overlap hypothesis assumes that amplitude of the 'true' positivity P3 does not vary during NoGo trials with small or large errors. It appears unlikely that motor related cortical activity contributes to the observed amplitude differences, either between 'correct' and 'incorrect' NoGo trials or between 'incorrect' trials with small or large errors. In the present study, onset and peak latency of the amplitude difference between 'incorrect' and 'correct' NoGo trials, relative to S2 onset, were about 230 ms and 300 ms, respectively. In contrast, with finger movement for 'incorrect' NoGo trials, onset and peak latency of contralateral inter-hemispheric asymmetry in the lateralized readiness potential (LRP) occurred at about 85 ms and 190 ms following S2. The latter indicates that motor related cortical activity occurred earlier. Furthermore, the absence of movement related lateralization in the LRP with eye movement questions whether a correlate of motor related cortical activity as found during finger movement also exists with saccadic eye movement. Nevertheless, the amplitude differences also were present in the eye movement conditions.

Kopp et al. (1996b) noted that the similarity in waveform, latency and scalp topography of component N2 on 'correct' NoGo trials and component N_e during NoGo 'error' trials suggests that both components may reflect similar cortical mechanisms. In the present study, morphology, latency and topography also were very similar for both ERP components. In addition, the present results suggest a progressive enhancement of component N_e with larger response errors. These observations support the hypothesis proposed by Kopp et al. (1996b), that the N2 and N_e may be equivalent with respect to their underlying cortical processes. However, as evidence against this hypothesis, Falkenstein et al. (1995) observed an error related negativity on 'incorrect' NoGo trials following visual as well as auditory NoGo stimuli; an N2 Go/NoGo effect only was found with visual stimuli.

3.4.4. Stimulus versus response synchronized averaging

Amplitude of component N_e was comparable in the stimulus and response aligned averaged cortical activity, although the N_e with eye movement appeared somewhat more smeared in the response locked averages. When trials with early and late motor response onset were compared, N_e peak latency was similar in the stimulus synchronized averages. N_e onset latency with stimulus aligned averaging was prolonged for trials with late response onset. With response synchronized averaging, N_e onset as well as peak latency were shorter for ERPs averaged across trials with late motor response onset. The latter findings suggest that component N_e in the present study was not completely time-locked either to the imperative Go/NoGo stimulus or to motor response onset. The N_e appeared to be related more closely to the stimulus. However, such inferences should be taken with caution. First, smearing of ERP components in stimulus or response aligned averages may be negligible as variance in motor response onset is not very large compared with temporal evolution of the ERP waveforms. Second, morphology and latency values of component N_e may be modified in the stimulus and response synchronized averages due to different temporal overlap with other stimulus or response aligned ERP components. The present results are in accordance with Falkenstein et al. (1991), who also observed that the N_e was not

perfectly related either to stimulus or response onset. However, Falkenstein and colleagues did find, in contrast to the present study, that the N_e tended to be time-locked more closely to the overt response. Bernstein et al. (1995) similarly suggested that the N_e represents a detection process which is related more directly to a comparison of the desired motor response with the response actually initiated, rather than to a comparison of the expected stimulus and the actual stimulus. In either study cited, the N_e was evaluated in choice reaction time tasks including a selection between several response alternatives. The present observation, that the N_e appeared to be time-locked more closely to the imperative stimulus, may indicate that a comparison between the anticipated and actual stimulus is relatively more important in a Go/NoGo task, as employed in the current study, including a choice of whether to execute or withhold a given motor response. However, the finding of a more pronounced N_e on NoGo trials with larger errors suggests that cortical processing underlying the N_e in the present study also incorporated information concerning motor response preparation.

3.4.5. Lateralized readiness potential

During finger movement, a preponderance of cortical activity over the hemisphere contralateral to the active finger was evident in the LRP profiles across central cortical areas (C' and C"). Previously published reports have proposed that inter-hemispheric lateralization with hand movement primarily reflects differential activation of pre-central left and right hand motor cortices (Bötzel et al., 1993; Böcker et al., 1994; Praamstra et al., 1996). As such, the LRP may be regarded as an index of central response preparation. Herein, inter-hemispheric lateralization was largest for motor actions on Go trials. On 'incorrect' NoGo trials, an initial development of contralateral lateralization also was evident, while a tendency toward contralateral response dominance was noted on 'correct' NoGo trials. The latter observations indicate that cortical movement preparation mechanisms were activated on 'incorrect' NoGo trials and also, to a lesser extent, on 'correct' NoGo trials. The development of contralateral cortical response lateralization appeared interrupted, suggesting that central response activation processes may have been inhibited on NoGo trials (see also De Jong et al., 1990). In accordance with a recent study by Wauschkun et al. (1997), inter-hemispheric lateralizations were absent during saccadic eye movement (see also chapter 2).

3.4.6. Conclusion

For finger movement and saccadic eye movement, comparable differences in morphology, amplitude and scalp topography of ERP components N2 and P3 were observed between Go and NoGo trials. In addition, for both movement modalities, a similar 'error negativity' (N_e) was found on 'incorrect' NoGo trials. These findings suggest that the cortical activity underlying component N_e and the observed N2 and P3 Go/NoGo effects, reflect general, non-effector specific, processing mechanisms associated with detection and/or suppression of an inappropriate tendency to respond.

4

Perceptual and motor contributions to performance and ERP components after incorrect motor activation in a flanker reaction task

Abstract

The purpose of this study was to evaluate contributions of response and perceptual processes to reaction performance in a flanker reaction task and to investigate whether event related potential (ERP) component N2 and error negativity N_e represent similar or functionally distinct cortical mechanisms.

ERPs, lateralized readiness potentials (LRPs) and reaction performance were measured in a flanker paradigm with arrows as targets and congruent or incongruent flankers. Squares were used as neutral flankers. Target color signaled a response of the hand indicated by (PRO) or against (ANTI) the target arrow's pointing direction.

On both PRO and ANTI conditions performance was facilitated by congruent and impaired by incongruent flankers. In the ERPs on trials with late response errors an N2 was evident before an N_e. In addition, ERPs on correct trials showed an N2 particularly after incongruent flankers on PRO but for each flanker type on ANTI conditions. On incongruent ANTI trials two successive response conflicts occurred but only a single N2 appeared.

The results indicate that differences in perceptual processing contribute significantly to the flanker effects on task performance and provide further evidence that N2 and N_e represent different cortical mechanisms. The data also suggest that N2 is not a real-time correlate of incorrect response suppression.

4.1. Introduction

The question whether separate stages in the human information processing system communicate with each other in a continuous manner or whether stages transmit information to other processing stages only if they are finished has been examined in a number of studies (Smid et al., 1991; Smid et al., 1992; Smid et al., 1996; Smid and Heinze, 1997). Important evidence that continuous communication exists comes from experiments which show that motor response activation can occur before stimulus evaluation has completed (Coles et al., 1985; Coles et al., 1988; Gratton et al., 1988; Smid et al., 1990). This preliminary motor activation is typically observed in a flanker reaction paradigm (Eriksen and Eriksen, 1974). The original paradigm consists of a bimanual choice reaction time task in which a target letter presented in the center of a five letter array signals a movement of the right or left hand (e.g., *S*: right hand; *H*: left hand). Distractor letters are either identical to the target (congruent flankers: *SSSSS* or *HHHHH*) or call for an opposite hand response (incongruent flankers: *HHSHH* or *SSHSS*). Consistently, reaction times in these tasks are found to be increased after incongruent flankers. Eriksen and co-workers argued that this flanker effect may result from competition at the motor response level. According to their continuous flow model, motor responses are activated as soon as stimulus information becomes available. When more flanker than target letters are presented motor activations are initially based on flanker identity. Gradually, when the central target letter is perceived, activation in accordance with the target becomes more important. Reaction times can be delayed by incongruent flanking elements as a result of a conflict between flanker and target based motor responses. The concept of early incorrect motor activation on incongruent flanker trials has been confirmed by the observation of an initial short-lasting positive deflection of the lateralized readiness potential (LRP) waveform (Gratton et al., 1988; Kopp et al., 1996a, Kopp et al., 1996b; Praamstra et al., 1998). The LRP positivity indicates that during a brief period before activation of the correct hand, the motor cortex corresponding to movement of the incorrect hand is activated stronger than the motor cortex controlling the correct hand (Gratton et al., 1988). However, in addition to the above described influence on processing at the motor activation level, flanker induced differences in perceptual processing also may contribute to the flanker effect on reaction performance (Eriksen and Schultz, 1979; Hoffman, 1979; Duncan and Humphreys, 1989; Smid et al., 1991). That is, performance may be slowed after incongruent flankers because recognition of the central target takes longer when flankers and target are dissimilar. The proposal of differences in stimulus evaluation is in line with findings of delayed peak latency values of the 'P300' event related potential (ERP) component on incongruent compared with congruent flanker trials (Coles et al., 1985; Smid et al., 1990; Praamstra et al., 1998). P300 latency has been proposed as a physiological marker of perceptual processing time (Donchin, 1981; Magliero et al., 1984; Mulder, 1986; Donchin and Coles, 1988).

In the ERP waveforms recorded on correct trials, with movement of the correct hand only, typically a frontal negative ERP component is observed which is most pronounced following incongruent flankers (Kopp et al., 1996a; Kopp et al., 1996b). As there is support for activating an incorrect hand response after incongruent flankers, the

component presumably corresponds to the frontal negative N2 observed after NoGo stimuli in Go/NoGo reaction time tasks (Simson et al., 1977; Eimer, 1993; Falkenstein et al., 1999; Van 't Ent and Apkarian, 1999). The NoGo-N2 has been associated with motor inhibition processing (Jodo and Kayama, 1992; Kopp et al., 1996b). A negative component also is found on error trials in which movement of the incorrect hand is evident. This component has been labeled 'error-related negativity' (ERN: Gehring et al., 1993) or 'error negativity' (N_e: Falkenstein et al., 1991). In the present paper the term N_e will be used. The N_e has been related to error detection and/or error inhibition processing (Falkenstein et al., 1991; Gehring et al., 1993; Falkenstein et al., 1995; Scheffers et al., 1996). From the finding that the N2 and N_e had similar latencies and showed comparable waveforms and scalp distributions, Kopp et al. (1996a, 1996b) concluded that these components may correspond to the same underlying cortical mechanism. However, Falkenstein et al. (1999) found in a Go/NoGo task that the N2 varied with stimulus modality (visual/auditory) and task performance (high/low error rates) whereas the N_e did not. Furthermore, Falkenstein and colleagues did find a difference in scalp topography, with N_e exhibiting a more central distribution than N2. Based on these results Falkenstein et al. (1999) suggested that the N2 and N_e reflect different cortical mechanisms. In addition, Falkenstein et al. (1999) correctly indicated that if the N2 and N_e represent functionally distinct mechanisms, an N2 should be present also on error trials before an N_e. However, clear evidence for an N2 on error trials was not found. Falkenstein and co-workers explained this negative result by noting that because the N_e on error trials occurs only slightly later than the N2 on correct trials, a possible N2 on error trials would be covered by the leading flank of the N_e.

To summarize, the introduction of flanker stimuli can influence processing at the motor response activation level and at the perceptual level. In the standard flanker task these effects work in the same direction inducing slowed task performance on incongruent flanker trials. Therefore, it remains unclear whether the origin of the flanker effect on reaction performance is predominantly located at the motor activation or at the perceptual level. The question whether ERP components N2 and N_e relate to the same underlying cortical mechanism or represent functionally distinct mechanisms also is still under debate. There is accumulating evidence that the N2 and N_e represent different cortical processes. Further support for this would be obtained when in the ERPs on error trials an N2 is found preceding an N_e.

In the present study a flanker reaction task was employed to examine the above questions. The test paradigm was a modified version of the original flanker task. Instead of letters with random response allocation, arrowheads pointing to the left or right were used as target and flankers. The use of arrows ensures a more straightforward relation between stimulus and hand to be moved. Flanker arrows could point either in the same (congruent) or opposite (incongruent) direction as the target arrow. To measure facilitation and interference effects of the flankers separately, a neutral flanker condition also was included. In addition to maximize the influence of the flankers, the flanker array was presented shortly before onset of the target stimulus. The most important design modification however was the introduction of a color coded target stimulus. The color coded target was implemented to differentiate between the effects on reaction

performance induced by processing at the motor activation and perceptual level. The central target was filled with one of two possible colors. One of these colors occurred more often and if the target appeared in this color a movement of the hand indicated by the pointing direction of the target arrowhead was to be made (target arrow to the left: left-hand; target arrow to the right: right-hand). However, if the target appeared in the other less frequent color a movement of the hand against the target arrow was required (target to the left: right hand; target to the right: left hand). The influence of the flankers on perceptual processing depends on differences in spatial geometry of the stimulus displays and therefore should not depend on target color. However, the effect of flanker triggered motor activations is expected to be reversed for the two color conditions. It was anticipated that the flanker stimuli would in general induce activation of the hand indicated by the flanker arrow's pointing directions. Movement of the hand in accordance with arrow direction was required on most trials. Furthermore, the flankers appeared earlier than the target and therefore the target's fill color was not yet known at the moment of flanker onset. For the frequent color condition with a required movement of the hand indicated by the target arrow this initial flanker triggered activation would be correct on congruent and incorrect on incongruent trials, like in the original flanker task. However for the infrequent condition with movement of the hand against the target arrow's direction, the flanker effect would be reversed with incorrect motor activation triggered by congruent and correct activation triggered by incongruent flankers.

The introduction of a multi-attribute target also allows for further investigation of the relation between N2 in the ERPs on correct trials and component N_c in the ERPs on trials with movement errors. Earlier work has shown that N_c is time-locked more closely to the motor response than to the stimulus, peaking shortly (in general earlier than 150 ms) after the onset of peripheral incorrect motor activation (Falkenstein et al., 1991; Falkenstein et al., 1999; Leuthold and Sommer, 1999). Therefore, component N_c is likely to appear at the same latency as the N2 because errors usually are early premature motor activations occurring at about or just before the time at which the N2 is observed. In the present experimental task incorrect hand movement can be induced not only by the flankers but also by partial information about the target stimulus (i.e., target arrow direction). In particular in the condition with the infrequent color, responses of the hand indicated by the target arrow can be activated before information on the combination of target direction and color signals the correct opposite hand. These target direction based movement errors occur later than flanker triggered errors and in the ERPs for trials with these late movement errors the N_c is expected to be delayed. Consequently, overlap of a possible N2 by the N_c component is reduced and the N2 should be more conspicuous. That is, when the N2 and N_c in fact do reflect different cortical mechanisms.

4.2. Methods

4.2.1. Subjects

Ten, right-handed, subjects participated in the study (7 males, 3 females; age range 23-53, mean age 31.9 yrs; three of these subjects also participated in the studies of chapters 2 and 3). Informed consent was obtained from each subject; experimental

protocols were approved by the ethics committee of the Erasmus University Medical Faculty.

4.2.2. Stimulus and Procedure

Subjects sat in a comfortable chair with arms supported by arm rests, hands positioned palm down, facing a computer screen positioned at 1 m distance. In the center of the screen a target stimulus was displayed consisting of an arrowhead pointing to the left or right (Fig. 1). The color of the central arrow, superimposed on a dark background, was either green or red. When colored green (PRO condition), subjects were required to extend the index finger of the hand indicated by the arrow as quickly as possible. When red (ANTI condition), a response of the hand against the arrow's direction was required. An array of gray colored flanker arrows surrounded the central target. The flanker arrows pointed either in the same (congruent) or opposite direction (incongruent) as the target. A neutral condition was included with squares as flankers. Target and flanker arrowheads consisted of isosceles triangles with sides subtending 1°. The size of the squares was selected such that squares and arrows contained equal amounts of pixels. Side-to-side distance between target and flankers was 0.1°. The start of an individual trial was indicated by the appearance of a central fixation cross. After 500 ms, the central cross was replaced by an array of flanker stimuli. The target stimulus appeared 100 ms later and was displayed for 50 ms. Subsequently target and flanker stimuli were removed. Two and a half seconds following target stimulus offset, visual feedback was provided indicating whether or not subjects initiated the appropriate motor action within 600 ms following target stimulus onset. The time interval between successive trials was randomized between two and three seconds.

Prior to the experiment, each subject completed a 15 min practice session to become familiar with the experimental protocol. The main experiment was performed in 6 blocks of 200 trials each. Congruent, neutral and incongruent flanker arrays were presented in random order. PRO and ANTI conditions were administered in pseudo-random order, with 70 % and 30 % probability for the occurrence of a PRO (green target) or ANTI (red) stimulus, respectively.

4.2.3. Recording

Electro-encephalographic (EEG) activity was recorded from five scalp sites, referred to linked earlobe electrodes. Midline electrode sites Fz, Cz and Pz were positioned according to the standard 10-20 system (Jasper, 1958). Lateral electrode sites C'3, C'4, were placed 1 cm anterior to landmarks C3 and C4 of the 10-20 system (e.g., Grünewald-Zuberbier et al., 1981). Electro-myographic activity (EMG) was recorded from electrode pairs covering left and right index finger extensor muscles. For monitoring eye movements, electro-oculography (EOG) was recorded, in bipolar derivation, from electrodes positioned above the nasion and at the outer canthus of the right eye. EEG and EOG were amplified with band-pass filter settings at 0.032 - 100 Hz; EMG was high-pass filtered at 5.2 Hz. Analog to digital conversion was performed at 250 Hz with 12 bit digital resolution.

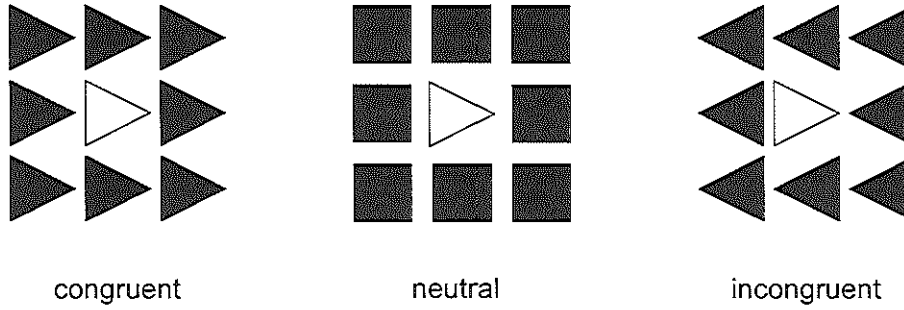


Figure 1: *Experimental setup. Visual stimulus consisting of a central target arrowhead surrounded by task-irrelevant flanker stimuli. For illustrative purposes, flanker array and target stimuli are depicted in black and white, respectively. The actual color of the flankers was gray, superimposed on the dark background of the computer screen. The central arrowhead was colored green or red. Green target stimuli instructed a movement of the hand indicated by the direction of the target arrow (PRO condition), red target stimuli signaled a response of the opposite hand (ANTI condition).*

4.2.4. Data analysis

4.2.4.1. Response accuracy and motor response latency

Various combinations of successive incorrect and correct hand activations were observed following target stimulus onset. Correct trials with a response of the signaled hand and no response related activity for the incorrect hand were found on 68% of the total number of trials. Error trials in which a correct hand response was preceded by a response of the incorrect hand were noted on 21 % of the trials. Analyses in the present study focused mainly on these two types of trials. The remaining 11% included trials with incorrect hand responses that remained uncorrected during the one second post-stimulus evaluation period, correct hand responses followed by activation of the incorrect hand and various other infrequent response combinations. For each subject and condition, correct trial scores were obtained as the number of correct trials divided by the total amount of trials for the given subject and condition. Mean onset latencies of incorrect and correct hand responses also were determined. Motor response latency was defined as the time interval between onset of the central target stimulus and onset of motor response activity, determined off-line by superimposing a vertical hairline cursor on the recorded EMG traces (Barrett et al., 1985). Statistical analysis on correct trial scores and response onset latencies was performed by means of repeated measures analysis of variance (ANOVA) with within-subject variables PRO vs. ANTI (PRO vs. ANTI condition) and Flanker Type (3 levels: congruent, neutral, incongruent).

4.2.4.2. Lateralized readiness potential (LRP)

Motor related inter-hemispheric amplitude asymmetry was evaluated by means of the lateralized readiness potential (LRP) measure derived from ERPs at electrode

sites C'3 and C'4 (e.g., De Jong et al., 1988; Gratton et al., 1988). Previous reports have indicated that inter-hemispheric lateralization with hand movement primarily reflects differential activation of pre-central left and right hand motor cortices (Bötzel et al., 1993; Böcker et al., 1994; Praamstra et al., 1996). As such, the LRP may be considered a measure of central motor response activation. ERPs from the hemisphere ipsilateral to the target arrow's pointing direction were subtracted from ERPs contralateral to target arrowhead direction and difference waveforms were averaged across trials with right- or leftward pointing target stimuli. Consequently, in the present study, correct motor activation is evident as a negative LRP asymmetry on PRO and a positive LRP asymmetry on ANTI trials. LRP waveforms were digitally low-pass filtered at 6 Hz. LRP onset latencies were evaluated by means of a jackknife-based procedure (Miller et al., 1998). For each stimulus condition latencies were determined at which LRP deflections reached a predefined criterion value. Linear interpolation between data samples was applied to estimate the time sample at which LRP asymmetry exactly equaled criterion threshold. The results reported in the present study are obtained with relative thresholds computed separately for each stimulus condition. However, comparable results were obtained when a fixed threshold across conditions was used. Inspection of the LRP profiles indicated that differences in LRP onset latency values between experimental conditions were larger at smaller LRP asymmetry values. Therefore, to optimize detection of onset latency differences, a relatively low criterion value equal to 20% of maximal LRP amplitude was used (Miller et al., 1998). When criterion values were satisfied by noise, as assessed by means of visual inspection, computerized identification was re-run within a more restricted time window. LRP amplitude values were calculated across fixed 50 ms time windows. These were centered on the latencies at which the deflections were maximal in the LRP profiles derived from ERPs averaged across subjects. LRP amplitude values were measured relative to mean LRP asymmetry across a 100 ms time interval centered on target stimulus onset, or, when preceded by opposite side response preparation, mean LRP amplitude across a 50 ms interval centered on maximal opposite LRP asymmetry. Earliest task related LRP deflections started at about 80 ms following target stimulus onset. LRP onset latency values were analyzed statistically by means of planned pair-wise comparisons (Miller et al., 1998). LRP amplitudes values were evaluated by repeated measures ANOVA with within subject variables PRO vs. ANTI and Flanker Type.

4.2.4.3. Event related potentials (ERPs)

For each subject and experimental condition, stimulus and motor response synchronized averaged ERP profiles were constructed. Trials with artefacts including eye movement activity, amplifier clipping, extensive muscle activity or electro-physiological drift were rejected. Averages subtended from 200 ms preceding to one second following central target stimulus or motor response onset. The first 100 ms of each epoch was used as pre-stimulus or pre-response baseline. Averaged ERPs were computed separately for correct trials, with no response related EMG activity on the incorrect side, and for error trials, with incorrect hand activation preceding correct hand movement. Determination of latency values of ERP components, relative to target

stimulus onset, was facilitated by superimposed vertical cursor hairlines on the averaged ERPs. Component latencies were measured at the electrode site where the component showed maximal amplitude. Latency of positivity P3 in the ERPs was determined on an individual trial basis from the cortical activity recorded at Pz. For this, first the ERP waveforms were digitally low-pass filtered at 6 Hz. Subsequently P3 latency was measured as the time at which the ERPs following stimulus onset showed maximal positivity (peak-picking at Pz). Component amplitudes were calculated by averaging ERP data samples within predefined 50 ms time windows. Time windows, for each individual subject, were centered on the latency at which component amplitude was maximal in the recorded cortical activity averaged across experimental conditions. Amplitudes either were measured relative to pre-stimulus (or pre-response) baseline or with respect to amplitude of the preceding ERP component, as indicated. Latency and amplitude values of ERP components at midline electrode sites were evaluated statistically by means of a three-way repeated measures ANOVA design. Within-subject variables included PRO vs. ANTI, Flanker Type and Electrode (Fz, Cz, Pz). For all statistical analyses, Bonferroni's correction method was implemented to allow for multiple comparisons. When applicable, degrees of freedom were adjusted conform the method proposed by Geisser and Greenhouse (1958). Uncorrected degrees of freedom are reported, however, to facilitate interpretation of the statistical design.

4.3. Results

4.3.1. Task performance

Correct trials scores and mean onset latencies of motor responses on correct trials are summarized in Table 1. Statistical analysis indicated that correct trial scores were reduced on ANTI compared with PRO conditions ($F(1,9) = 51.75$, $p < 0.001$). Furthermore, a significant main effect for variable Flanker Type ($F(2,18) = 19.38$, $p < 0.001$) revealed significant benefits ($F(1,9) = 7.22$, $p = 0.025$) and costs ($F(1,9) = 14.41$, $p = 0.004$) for correct trial scores on congruent and incongruent flanker trials compared with neutral trials. Onset latencies of correct hand motor activations were significantly shorter on PRO compared with ANTI conditions ($F(1,9) = 195.86$, $p < 0.001$). In addition, correct motor activation started earlier on congruent ($F(1,9) = 13.98$, $p = 0.005$) and later on incongruent ($F(1,9) = 25.49$, $p = 0.001$) trials than on neutral flanker trials. The influence of the flanker manipulation on correct trial scores and motor activation latencies was comparable for PRO and ANTI conditions (PRO vs. ANTI by Flanker Type interactions: not significant).

	correct trial score (%)		response latency (ms)	
	PRO	ANTI	PRO	ANTI
congruent	81 ± 13	60 ± 22	327 ± 53	422 ± 64
neutral	76 ± 13	56 ± 20	339 ± 50	427 ± 58
incongruent	72 ± 17	46 ± 22	361 ± 50	445 ± 63

Table 1: *Correct trial scores and mean motor response latencies (± standard error of the mean) for signaled hand activations on correct PRO and ANTI trials.*

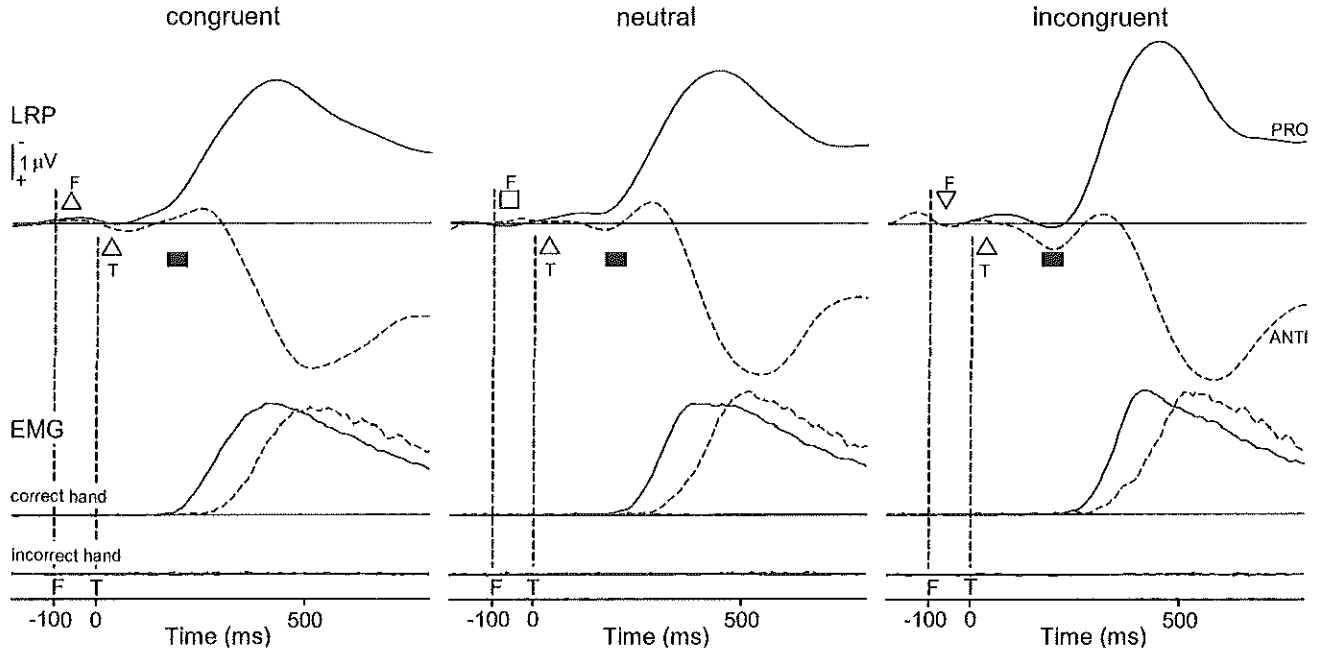


Figure 2: *LRP waveforms derived from stimulus synchronized ERPs on PRO (solid) and ANTI (dashed) stimulus conditions. Accompanying correct and incorrect hand motor response activity also is shown (EMG: bottom traces). Left panel: congruent; middle: neutral ; right: incongruent. Flanker array (F) and central target (T) onset are denoted above the time axes. Up- or downward arrow symbols in the LRP panels indicate the direction of LRP deflections induced by the flanker and target arrows when responses of the hand indicated by arrow direction are activated. A square at flanker onset for neutral trials means no induced activation. Horizontal bars below the LRP profiles indicate the time window, subtending from 168 to 216 ms post central target onset, used to compute mean values of flanker related LRP deflections.*

4.3.2. Lateralized readiness potential (LRP)

Fig. 2 shows stimulus aligned LRP profiles derived from ERPs on correct trials, averaged across subjects, on PRO (solid) and ANTI (dashed) stimulus conditions. Motor response activation (EMG) is also depicted. Initial negative and positive deflections in the LRPs on congruent (left panel) and incongruent (right panel) flanker trials starting at about 80 ms following target stimulus onset indicate that first responses of the hand indicated by flanker arrow direction were prepared. The top left of Table 2 shows mean amplitudes of initial LRP deflections during a fixed time window subtending from 168 to 216 ms post target onset. This 48 ms interval, also indicated by filled horizontal bars below the LRP profiles in Fig. 2, is centered on the latency at which maximal incorrect LRP asymmetry is evident on incongruent PRO trials. Statistical analysis supported the presence of a flanker effect on LRP values in this window ($F(2,18) = 6.41$, $p = 0.008$). The asymmetries were not significantly different between PRO and ANTI conditions. At about 190 ms following target stimulus onset final correct, negative, LRP deflections are evident on PRO conditions. At this time negative LRP deflections are also observed for each flanker type on ANTI conditions. These results indicate that on both PRO and ANTI conditions movement of the hand indicated by the target's pointing direction was prepared after flanker induced motor activation. The bottom left part of Table 2 lists onset latencies of negative LRP deviations, computed as the time at which the deflections equaled 10% of maximum correct LRP asymmetry on PRO trials. A 10 instead of 20% relative threshold was used for the computation of onset latencies as 20% maximal LRP asymmetry was not always attained by the smaller LRP negativities on ANTI trials. Onset latencies are slightly longer on ANTI than on PRO conditions, in particular for congruent and neutral flanker trials. However, the latency differences were not statistically significant. For ANTI conditions, maximum amplitudes of negative LRP lateralization with congruent, neutral and incongruent flankers were -0.37 ± 0.46 μV, -1.29 ± 1.65 μV and -1.89 ± 1.86 μV. Although the amplitudes are smaller on congruent and larger on incongruent flanker trials than on neutral trials, a statistically significant effect of flanker type on these LRP asymmetry values was not found. The bottom right of Table 2 lists onset latencies of final correct, negative, LRP deflections on PRO and final correct, positive, LRP deflections on ANTI conditions. Correct LRP asymmetry started later on ANTI than on PRO trials ($F(2,18) = 148.30$, $p < 0.001$). In addition, compared with neutral trials LRP onset latencies on PRO conditions were shorter on congruent ($F(1,9) = 10.46$, $p = 0.010$) and longer on incongruent flanker trials ($F(1,9) = 48.37$, $p < 0.001$). Correct activation on ANTI conditions also started later on incongruent than on neutral trials ($F(1,9) = 34.46$, $p < 0.001$) but a significant difference between congruent and neutral flanker trials was absent.

The LRP waveforms analyzed are derived from averaged ERP data. Therefore, early correct LRP deflections on congruent PRO and incongruent ANTI trials may result from inclusion of trials with flanker triggered motor activations which happen to be correct for these conditions. To examine this, LRP waveforms were recalculated and derived from trials with correct motor responses starting later than 300 ms post target. Resultant LRP profiles on PRO and ANTI conditions with congruent and incongruent flankers are depicted in Fig. 3. Although flanker triggered hand movement is likely to

be absent on these trials, the LRP waveforms nevertheless show early flanker related up- and downward deflections. Amplitude values of LRP deviations from 168 to 216 ms post target, also used for assessing flanker induced asymmetries across all trials, are listed in the top right of Table 2. The LRP deflections during this interval again showed a significant influence of the flanker manipulation ($F(2,18) = 5.44$, $p = 0.028$).

	all		resp. lat. > 300 ms	
	PRO	ANTI	PRO	ANTI
congruent	-1.4 ± 1.2	-0.5 ± 1.2	-0.8 ± 1.6	-0.9 ± 1.7
neutral	-0.9 ± 0.9	0.3 ± 2.6	-0.2 ± 1.1	0.4 ± 3.1
incongruent	0.4 ± 1.4	1.5 ± 2.1	0.6 ± 1.2	1.5 ± 2.3
	10% max. asymm.[a]		20% max. asymm.	
	PRO	ANTI	PRO	ANTI
congruent	158 ± 20	190 ± 51	196 ± 14	320 ± 15
neutral	208 ± 9	226 ± 16	231 ± 10	344 ± 11
incongruent	249 ± 15	250 ± 25	270 ± 12	385 ± 15

[a] 10% of maximal LRP asymmetry on correct PRO trials.

Table 2: *Top: mean amplitudes of flanker induced asymmetries in the stimulus aligned LRPs during a time window subtending from 168 to 216 ms post target onset. Asymmetries are computed either for LRPs derived from all correct trials (left section), or from ERPs across correct trials with motor activation later than 300 ms post-target (right). Bottom left: onset latencies of negative LRP deflections reflecting activation of the hand signaled by target arrowhead direction. Onset latencies are determined with a fixed criterion threshold equal to 10% maximal LRP amplitude for the corresponding flanker condition on PRO trials. Bottom right: mean onset latencies of stimulus aligned LRP asymmetries associated with final correct hand activation. Onset latencies are defined as the time at which correct LRP asymmetry equals 20% of maximal LRP amplitude for the given condition.*

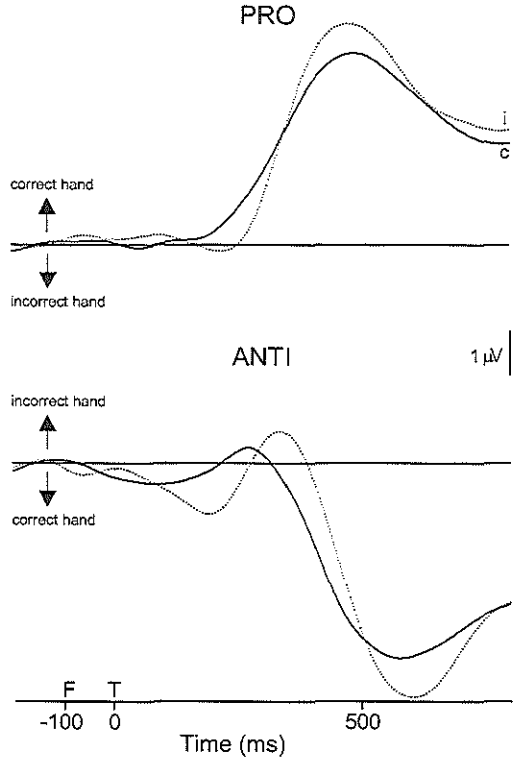


Figure 3: *Stimulus aligned LRP waveforms derived from ERPs on correct trials with onsets of motor activation later than 300 ms following target stimulus onset. LRPs are shown for congruent (c: solid traces) and incongruent (i: dotted traces) flanker conditions. Upper panel: PRO; bottom panel: ANTI. Initial up- and downward LRP deflections following target stimulus onset indicate flanker triggered hand activation after congruent and incongruent flankers, respectively. LRPs on ANTI trials clearly show selection of the hand indicated by target arrowhead direction (upward deflections) following flanker based motor activation.*

4.3.3. Event related potentials

Fig. 4 shows stimulus aligned ERPs on correct trials, at midline sites Fz, Cz and Pz, with congruent (solid traces), neutral (dashed) and incongruent (dotted) flankers. The components identified in the ERPs are illustrated for the cortical activity recorded at Cz. On PRO conditions (top) the sequence of components and effects of flanker type on these components resembled the findings reported by Kopp et al. (1996a). At about 150 ms post flanker onset an early negativity is evident with largest amplitude at parietal site Pz. This component, labeled N100, is followed by a frontal-central negativity N2b at around 290 ms. Similar to Kopp et al. (1996a), component N2b is

most negative after neutral flankers. Kopp and colleagues proposed that N2b possibly relates to the detection of perceptual deviation from prevailing stimuli. Therefore, N2b may be enhanced on neutral trials when squares as neutral flankers are presented in one-third and arrows as congruent or incongruent flankers are presented in two-thirds of the trials. After the N2b a positivity is observed peaking at 370 ms post-flanker onset. Kopp et al. (1996a) suggested that this positivity may relate to orienting behaviour in response to flanker array onset. About 120 ms later a second positivity, labeled P3, is observed. Component P3 is most pronounced at parietal site Pz and reduced in amplitude on congruent flanker trials. Finally, a distinct negativity N2 is evident preceding P3 specifically on incongruent flanker trials. In the ERPs on ANTI conditions (bottom) a comparable sequence of components is found. The averaged waveforms also show an N2 component which, in contrast to PRO conditions, is readily detectable also on congruent and neutral flanker trials. For component P3, a reduction in amplitude on congruent trials as observed on PRO conditions is absent on ANTI conditions.

Amplitude values of components N2 and P3 are summarized in the top panels of Table 3. Amplitude of the N2 was determined, peak-to-peak, with respect to the immediately preceding positive deflection in the ERPs. P3 amplitude was measured relative to pre-stimulus baseline. Statistical analysis indicated that N2 was more pronounced at frontal-central electrode sites Fz and Cz compared with parietal site Pz ($F(1,9) = 9.84$, $p = 0.012$). N2 amplitude was numerically, but not significantly, larger at Fz than at Cz. For the N2 components on ANTI trials a significant influence of the flankers was absent. In addition, these negativities were of equal size compared with the N2 on incongruent PRO trials. Analysis on P3 amplitude revealed a significant main effect for variable Electrode ($F(2,18) = 8.36$, $P = 0.003$). P3 was larger at Pz compared with Fz and Cz ($F(1,9) = 12.63$, $p = 0.006$). Main variables PRO vs. ANTI and Flanker Type were not significant. A significant PRO vs. ANTI by Flanker Type interaction also was absent. However, when PRO and ANTI conditions were analyzed separately an influence of flanker type was observed on PRO but not on ANTI conditions (PRO: $F(2,18) = 4.57$, $p = 0.048$; ANTI: $F(2,18) = 0.19$, $p = 0.83$).

Peak latencies for N2 and P3 are listed in the bottom panels of Table 3. Latencies of the N2 components on ANTI conditions were similar to N2 latency on incongruent PRO trials and did not show an influence of the flanker manipulation. For component P3 an effect of Flanker Type ($F(2,18) = 8.92$, $p = 0.002$) was found. P3 latency was enhanced on incongruent compared with congruent and neutral flanker trials ($F(1,9) = 15.35$, $p = 0.004$). A PRO vs. ANTI by Flanker Type interaction was absent but, when evaluated separately, the delay of component P3 on incongruent trials was significant for PRO conditions only (PRO: $F(1,9) = 18.04$, $p = 0.002$; ANTI: $F(1,9) = 1.01$, $p = 0.340$).

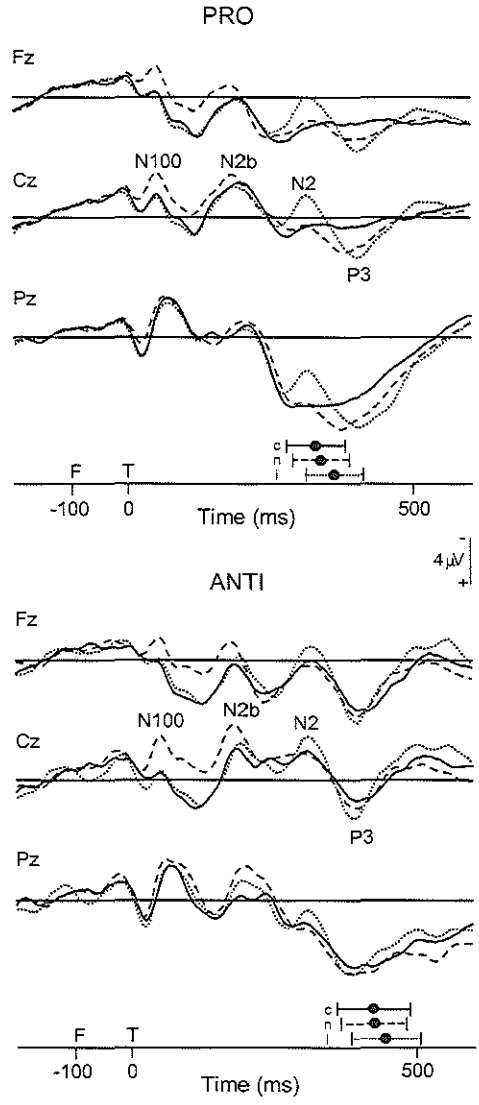


Figure 4: *ERPs averaged across subjects on correct PRO (top) and ANTI (bottom) trials for congruent (solid), neutral (dashed) and incongruent (dotted) flanker conditions. ERP profiles recorded at midline electrode sites Fz, Cz and Pz are depicted in a time window subtending from 200 ms preceding to 600 ms following target onset. Components identified in the recorded cortical activity are illustrated at Cz. Horizontal bars above the time axes indicate mean motor response onset latency ± standard error of the mean.*

	N2 (Fz)		P3 (Pz)	
	Pro	Anti	Pro	Anti
		Amplitude		
Congruent		-3.9 ± 3.9	5.9 ± 3.6	6.2 ± 5.4
Neutral		-3.3 ± 3.4	8.1 ± 4.0	6.8 ± 6.0
Incongruent	-3.1 ± 2.1	-4.4 ± 2.7	8.4 ± 5.1	6.4 ± 6.1
		Latency		
Congruent		308 ± 17	389 ± 11	398 ± 15
Neutral		315 ± 17	391 ± 18	399 ± 14
Incongruent	316 ± 14	315 ± 15	405 ± 18	402 ± 11

Table 3: *Mean amplitude (top) and peak latency (bottom) values of ERP components N2 and P3. Values are listed for electrode sites Fz and Pz, respectively. At these sites the components were most pronounced.*

4.3.4. Speed Accuracy Trade off functions

Speed accuracy trade off (SAT) functions were evaluated as an independent tool, in addition to LRP waveform analysis, for investigating the influence of stimulus processing on reaction behaviour (Smid et al., 1987; Gratton et al., 1988; Smid et al., 1990). To keep the duration of stimulus evaluation constant in relation to EMG onset, ratios between onset latency of first occurring EMG, correct or incorrect, and P3 latency were computed for each trial (Coles et al., 1985; Smid et al., 1987; Smid et al., 1990). Trials were classified into bins on the basis of EMG/P3 latency ratio and for each bin motor response accuracy was determined as the number of trials in which first EMG was correct divided by the total amount of trials for the given bin. SAT functions depicted in the top panel of Fig. 5 support the LRP results. On PRO conditions an effect of flanker type is visible for EMG responses emitted early relative to P3 latency. In the first ratio bin (EMG/P3 < .6), accuracy of first EMG is above 50% chance on congruent trials, approximately at 50% chance on neutral and below 50% chance level on incongruent flanker trials. For neutral and incongruent flanker trials, probabilities of correct EMG increase when EMG onset occurs later relative to P3 latency, until, on third and consecutive bins, accuracy levels are comparable to those on congruent flanker trials. A flanker effect on early motor responses is also evident on ANTI conditions. As for this experimental condition incongruent flankers indicate a correct motor response while congruent flankers call for incorrect response activation, accuracy in the first ratio bin is above 50% chance on incongruent and below chance on congruent flanker trials. For incongruent trials, a decrease in performance accuracy after the first bin indicates subsequent selection of the hand indicated by target arrowhead direction. Reversal towards an increase in correct EMG probability for trials in fourth and succeeding bins indicates that information about the conjunction of target arrow

direction and target color becomes available. On congruent trials, a rapid increase in motor response accuracy is noted after the first bin. Probability of correct first EMG is already above 50% chance in the third ratio bin and remains above chance in succeeding bins. This suggests an earlier start of hand activation in accordance with target identity on congruent trials. Accuracy on neutral flanker trials remains roughly in between probability levels on congruent and incongruent trials for each EMG/P3 latency bin.

As the width of the ratio bins was relatively small, the number of trials per subject was limited in several bins. To perform a reliable statistical analysis, trials were re-divided into a smaller number of groups. New SAT functions were derived after classifying the trials into four quartiles on the basis of EMG/P3 latency ratios for PRO and ANTI conditions, separately. Computed functions displayed at the bottom of Fig. 5 show the same pattern as the SAT profiles in the top panels. The effect of flanker type for early motor activations is less clear, however, in particular for ANTI conditions. Statistical analysis on response accuracy was performed by repeated measures ANOVA with within subject variables Flanker Type and EMG/P3 latency Quartile (four levels). For both PRO and ANTI conditions, significant main effects for variables Flanker Type (PRO: $F(2,18) = 18.93$, $p < 0.001$; ANTI: $F(2,18) = 7.66$, $p = 0.004$), EMG/P3 Quartile (PRO: $F(3,27) = 15.85$, $p < 0.001$; ANTI: $F(3,27) = 42.82$, $p < 0.001$) and significant Flanker Type by Quartile interactions (PRO: $F(6,54) = 26.38$, $p < 0.001$; ANTI: $F(6,54) = 4.23$, $p = 0.001$) were found. On PRO conditions, the effect of flanker type indicated that differences in accuracy levels between first and consecutive EMG/P3 quartiles were smaller on congruent ($F(1,9) = 14.87$, $p = 0.004$) and larger on incongruent flanker trials ($F(1,9) = 29.38$, $p < 0.001$) compared with neutral trials. In the first ratio quartile, probability of correct EMG was above 50% chance on congruent ($F(1,9) = 253.77$, $p < 0.001$) and neutral trials ($F(1,9) = 27.35$, $p = 0.003$) but not significantly different from chance on incongruent flanker trials. On ANTI conditions accuracy of motor responses in the first EMG/P3 quartile were at 50% chance for each flanker type. The development of correct response probability from first to second quartile on congruent and incongruent flanker trials differed significantly from neutral trials (congruent: $F(1,9) = 6.38$, $p = 0.032$; incongruent: $F(1,9) = 7.06$, $p = 0.026$). Consequently, accuracy of first EMG in the second ratio quartile was higher on congruent ($F(1,9) = 8.88$, $p = 0.030$) and lower on incongruent trials ($F(1,9) = 12.25$, $p = 0.014$) than on neutral flanker trials. On incongruent trials performance showed a stronger increase from second to third and fourth quartiles compared with neutral flanker trials ($F(1,9) = 6.73$, $p = 0.029$). A significant difference between congruent and neutral trials was not found. Finally, for responses in third and fourth ratio quartiles, a significant influence of flanker type on correct response probability was absent.

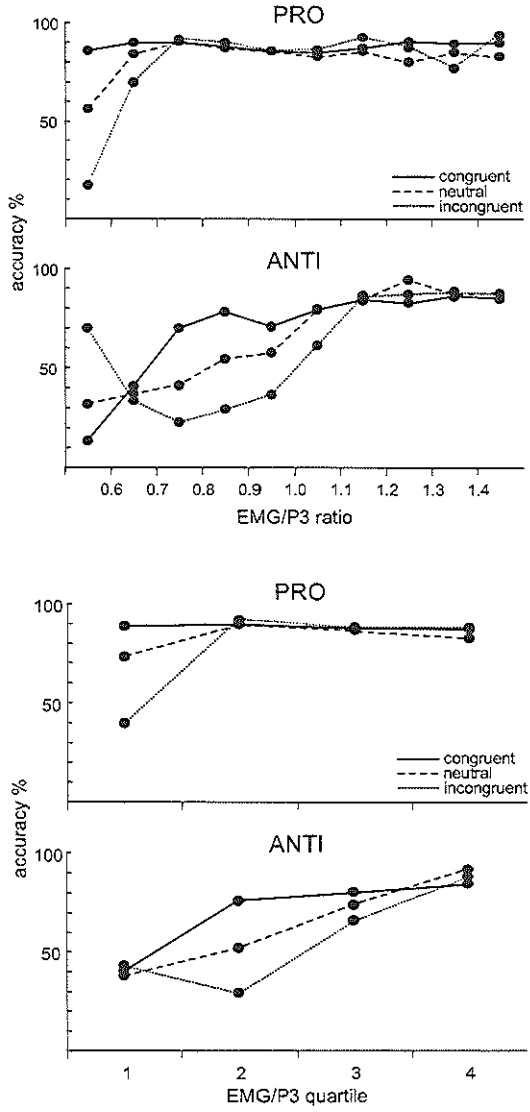


Figure 5: *Speed accuracy trade-off (SAT) functions on PRO and ANTI conditions with congruent (solid), neutral (dashed) or incongruent (dotted) flankers. SAT profiles are corrected for stimulus evaluation time (EMG/P3 ratio). Trials are either grouped in predefined EMG/P3 latency bins of size 0.1 (top two panels) or in four EMG/P3 ratio quartiles (bottom panels). For the ratio quartiles, 25, 50 and 75 percentiles were 0.70, 0.81, 0.95 on PRO and 0.79, 0.93, 1.18 on ANTI conditions. Accuracy in each bin is defined as the percentage of trials with correct first EMG.*

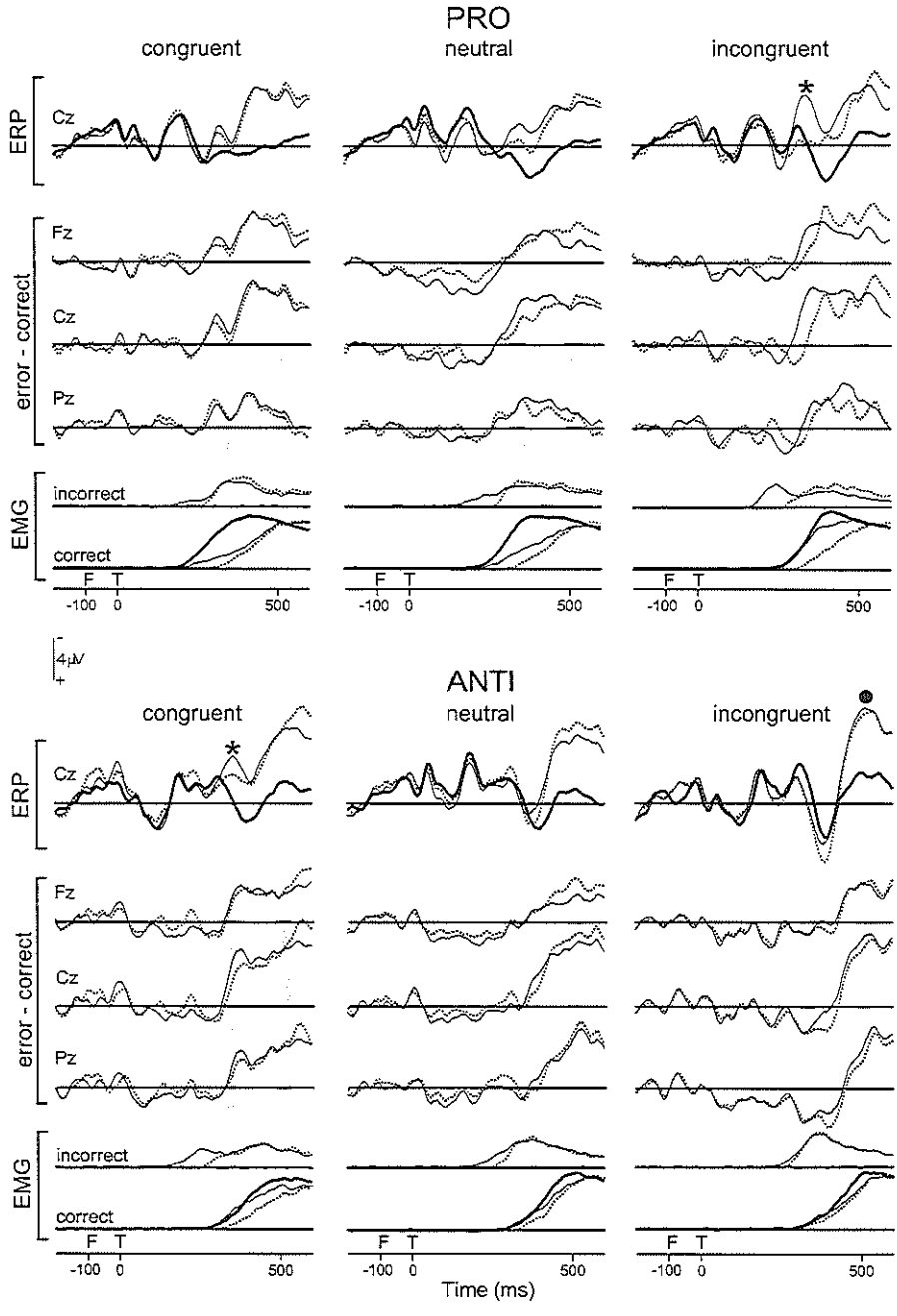
4.3.5. Error trials

4.3.5.1. Stimulus aligned ERPs

Waveforms at the top of each panel in Fig. 6 show stimulus aligned ERPs, recorded at vertex electrode Cz, on correct trials (bold) and on error trials (solid thin). In addition, dotted traces represent ERPs averaged across error trials with incorrect hand activation starting later than 265 ms post target onset. Inspection of EMG latency histograms indicated that onsets of incorrect hand activation showed a bimodal distribution with peaks separated at about this latency. Incorrect responses earlier than 265 ms are believed to consist primarily of flanker triggered motor activations because they were most common after incongruent flankers on PRO and congruent flankers on ANTI trials. EMG profiles at the bottom of each panel in Fig. 6 also show strongest and earliest incorrect hand activation for these experimental conditions (solid thin traces). ERPs on error trials show a negative enhancement compared with ERPs on correct trials, presumably corresponding to the error negativity N_e. In the ERPs across all error trials error negativity exhibits a bi-phasic pattern. A first negativity peaks slightly after the latency at which component N2 on correct trials is maximal and is evident most clearly on incongruent PRO and congruent ANTI trials (indicated by asterisks in Fig. 6). The second negative enhancement follows ERP component P3 and is about equally large across stimulus conditions, albeit most clearly defined on incongruent ANTI trials (filled dot in Fig. 6). In the ERPs across trials with flanker triggered errors excluded a reduction in amplitude of the first negative enhancement is evident, in particular on incongruent PRO trials. Below the ERP waveforms in Fig. 6 difference potentials are shown, for midline sites Fz, Cz and Pz, obtained by subtracting the ERPs on correct trials from ERPs averaged either across all error trials (solid) or across error trials with incorrect hand activation later than 265 ms post target (dotted). In the error minus correct waveforms ERP amplitude differences appear more like single negative enhancements, except for the congruent PRO condition. With all error trials included and pooled across flanker conditions difference potentials start at about 275 ms post target onset on PRO and 350 ms post target on ANTI conditions. On incongruent PRO trials onset of the negative difference is delayed when trials with errors beyond 265 ms post target are excluded. On congruent ANTI trials only a slight reduction of the initial enhancement is evident. A clear difference in onset latency compared with averages across all error trials is absent.

Amplitudes of the difference waveforms were calculated across two fixed 48 ms time windows. Intervals, indicated by grey vertical bars in Fig. 6, subtended from 316 to 364 ms following target stimulus onset for the early and from 492 to 540 ms following target onset for the late time window. The early window was centred on the maximum of the first negative enhancement in the cortical activity, across all error trials and subjects, in the incongruent PRO condition. The late window was centred on the maximum of the second negative displacement in the ERPs on incongruent ANTI trials. Fig. 7 shows computed difference amplitudes for PRO (top panels) and ANTI (middle) conditions. Statistical analysis revealed that error minus correct waveforms with all error trials included (filled symbols) differed significantly from zero during both early (circles) and late (squares) time windows (early: $F(1,9) = 20.64$, $p = 0.001$; late: $F(1,9)$

= 21.98, p = 0.001). Main effects for variables Electrode Site indicated further that the difference potentials were most pronounced at frontal-central sites Fz and Cz, with largest amplitude at Cz (early: $F(2,18) = 12.12$, $p < 0.001$; late: $F(2,18) = 11.02$, $p = 0.001$). Variables PRO vs. ANTI and Flanker Type were not significant. For the early time window also a significant PRO vs. ANTI by Flanker Type interaction ($F(2,18) = 4.38$, $p = 0.028$) was found. The interaction indicated that negativity during this interval was largest after incongruent flankers on PRO conditions but most pronounced after congruent flankers on ANTI conditions. In fact when tested separately, a significant difference potential during the early window was absent on congruent and neutral PRO trials and neutral and incongruent ANTI trials. Compared with averages across all error trials, negative differences for trials with motor response errors later than 265 ms (open symbols) were reduced during the early time window ($F(1,9) = 14.25$, $p = 0.008$) but not during the late window. Consequently, significant error minus correct differences were observed only during the late window ($F(1,9) = 21.91$, $p = 0.002$). Thus, on conditions where flanker triggered errors are virtually absent or when trials with early flanker triggered errors are excluded from averaging, error related negativity is evident only after the time at which the N2 component occurs, with ERP negativity comparable to correct trials during the N2 latency range.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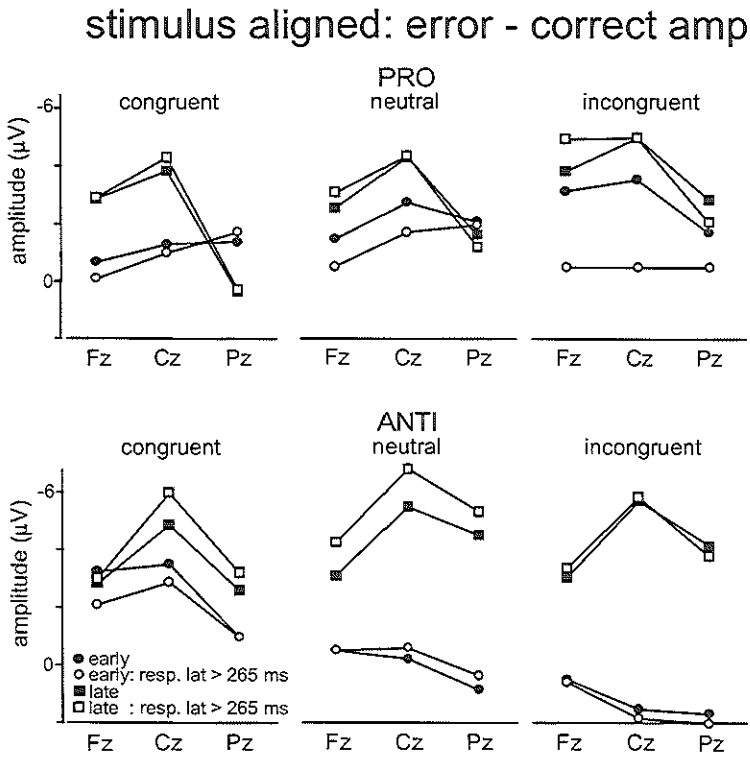
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early: resp. lat > 265 ms
late
late : resp. lat > 265 ms

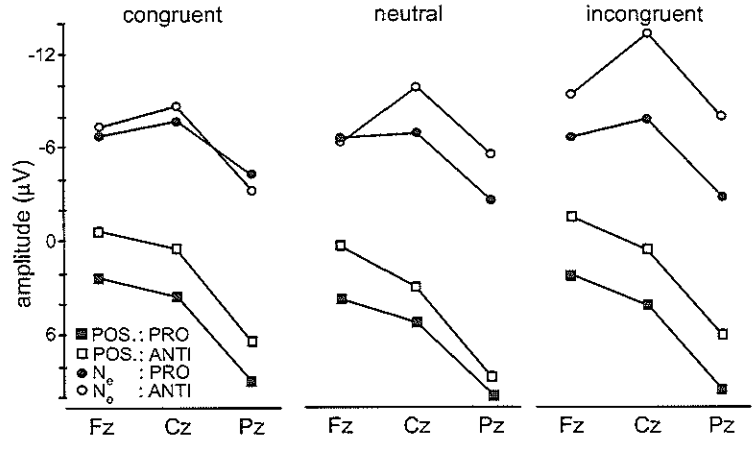
response aligned: ERP ampl.
congruent
neutral
incongruent
amplitude (μV)
-12
-6
0
6
POS.: PRO
POS.: ANTI
Ne : PRO
No : ANTI
Fz Cz Pz

Figure 6: *Top traces in each panel, for PRO (top) and ANTI (bottom) conditions indicate ERPs, recorded at Cz and averaged across subjects, on correct (bold lined) and error (thin) trials. Dotted waveforms depict averaged ERPs across error trials with incorrect EMG later than 265 ms post target onset. Left, middle and right panels represent congruent, neutral and incongruent flanker conditions, respectively. Compared with correct trials, ERPs on error trials exhibit a bi-phasic pattern of enhanced negativity. The first negative enhancement is marked by asterisks in the panels for incongruent PRO and congruent ANTI conditions. The second negative enhancement is indicated by a filled dot for the incongruent ANTI condition. Below the ERP waveforms, difference potentials are shown, for midline sites Fz, Cz and Pz, obtained by subtracting averaged ERPs on correct trials from ERPs averaged across all error trials (solid) or across error trials with incorrect motor activation later than 265 ms post target (dotted). Superimposed grey vertical bars indicate early and late time windows during which amplitudes of error minus correct difference waveforms were measured. At the bottom of each panel accompanying EMG for the correct and incorrect hand is depicted.*

Figure 7: *In the top and middle panels amplitude values of error minus correct difference waveforms are depicted for PRO and ANTI conditions, respectively. Difference potentials are shown either for all error trials (filled symbols) or for error trials with incorrect hand activation later than 265 ms post target (open). Left, middle and right panels show data for congruent, neutral and incongruent flanker conditions, respectively. Circles represent difference amplitudes measured during an early time window subtending from 316 to 364 ms post target onset. Squares indicate error minus correct differences during a late window from 492 to 540 ms post target. Bottom panels show maximum amplitude values of deflections in the response aligned ERP profiles on PRO (filled symbols) and ANTI (open) conditions. Squares represent amplitude values of positive deflections on correct trials, circles depict amplitudes of negativity N_e on error trials.*

4.3.5.2. Response aligned ERPs

In Fig. 8 response synchronized cortical activity, across subjects, on correct (bold) and error (thin) trials is depicted. ERPs on error trials are aligned on onset of initial incorrect motor response activation (t = 0 ms). On correct PRO trials, waveforms for each flanker condition consist of a single central-parietal positivity starting shortly before and peaking about 85 ms after response onset. ERPs on correct ANTI trials also show a positive deflection, largest at parietal site Pz. However, positivity is less well defined compared with correct PRO trials and, in particular at frontal-central electrode sites, appears disrupted by concurrent ERP negativity. In the ERPs on error trials an initial developing positivity also is evident for both PRO and ANTI conditions. However, at about 35 ms following incorrect response onset the positive deflections are abruptly ended due to onset of the N_e.

In the left of Table 4 peak latencies of the positive ERP deflections on correct trials, are listed. Statistical analysis indicated that latency values were comparable

between PRO and ANTI conditions and flanker types (variables PRO vs ANTI, Flanker Type and interactions: not significant). Peak amplitude values of the positivities, with respect to pre-response baseline, are depicted by squares in the bottom panels of Fig. 7. Amplitudes were larger on PRO (filled) compared with ANTI (open) conditions ($F(1,9) = 21.55$, $p = 0.001$). In addition, significant main effects for variables Electrode Site ($F(2,18) = 35.61$, $p < 0.001$) and Flanker Type ($F(2,18) = 4.70$, $p = 0.023$) were found. These indicated that positivities were largest at Pz and more pronounced on neutral compared with congruent and incongruent flanker conditions. In the right of Table 4 peak latencies of the N_e deflections on error trials are summarized. These were shorter on PRO than on ANTI conditions ($F(1,9) = 14.37$, $p = 0.004$). A significant main effect for variable Flanker Type ($F(2,18) = 4.57$, $p = 0.025$) indicated in addition that the N_e peaked earlier on congruent compared with neutral and incongruent trials. Amplitudes of the N_e, measured relative to the preceding positive deflection, are indicated by circles in the bottom panels of Fig. 7. The N_e was largest at the Cz electrode ($F(1,9) = 36.50$, $p < 0.001$) and, also primarily at Cz, more negative on ANTI (open circles) than on PRO (filled) trials (PRO vs. ANTI: $F(1,9) = 6.63$, $p = 0.030$; PRO vs. ANTI by Electrode Site: $F(2,18) = 9.23$, $p = 0.004$).

Finally, incorrect LRP and EMG on error trials also were analyzed. These were comparable across flanker types but, as for the N_e, were slightly larger on ANTI compared with PRO conditions (LRP ($\mu V \pm$ s.e.m): 1.3 ± 1.8 [PRO]; 2.4 ± 1.5 μV [ANTI]: $F(1,9) = 7.60$, $p = 0.022$; EMG: 16.4 ± 5.6 [PRO], 17.9 ± 6.5 [ANTI]: $F(1,9) = 6.39$, $p = 0.032$).

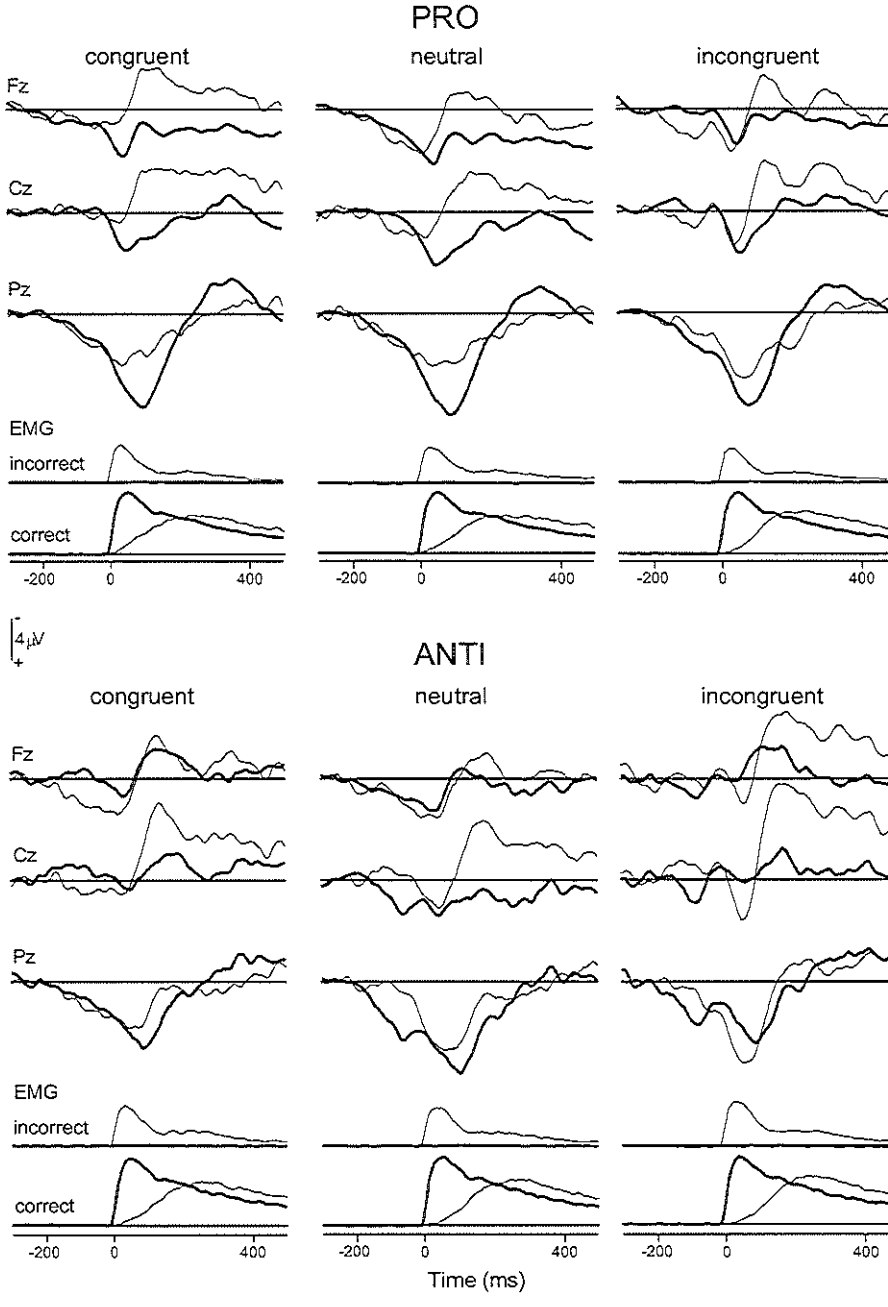
PRO
congruent
neutral
incongruent
Fz
Cz
Pz
EMG
incorrect
correct
-200
0
400
4 μV
ANTI
congruent
neutral
incongruent
Fz
Cz
Pz
EMG
incorrect
correct
-200
0
400
Time (ms)

Figure 8: *Response locked cortical response profiles at midline electrodes Fz, Cz and Pz, on correct (bold) and error (thin) trials, averaged across subjects. ERP profiles are depicted for PRO (top) and ANTI (bottom) conditions with congruent (left), neutral (middle) and incongruent (right) flankers. The time window subtends from 300 ms preceding to 500 ms following motor response onset (t = 0 ms). EMG traces show accompanying motor activity for the incorrect and correct hand, respectively. ERPs on error trials are aligned on onset of initial incorrect hand activation.*

	pos. on correct trials		N_e on error trials	
	PRO	ANTI	PRO	ANTI
congruent	86 ± 23	80 ± 22	106 ± 26	117 ± 18
neutral	81 ± 23	91 ± 17	113 ± 20	142 ± 26
incongruent	81 ± 22	79 ± 16	117 ± 19	142 ± 27

Table 4: *Left: peak latencies, determined at Pz and measured with respect to correct motor response onset, of positive deflections in the response aligned ERPs on correct trials. Right: peak latencies of error negativity N_e, determined at Cz, in the incorrect response aligned ERPs.*

4.4. Discussion

4.4.1. motor and perceptual processing

4.4.1.1. Task performance

In the present flanker task reaction times of correct hand responses were delayed and the amount of motor response errors was higher on ANTI compared with PRO conditions. In particular the large number of errors on ANTI conditions indicates that a tendency was present for the subjects to activate the hand indicated by the pointing direction of the target arrow. This was facilitated by the fact that PRO targets were presented more frequently than ANTI targets. Compliance with the task on PRO and ANTI conditions also may have differed due to the fact that stimulus-response mapping is more straightforward after PRO stimuli. Selection of the hand indicated by arrow direction is considered a population stereotype (Kornblum et al., 1990) and expected to require less effort than activating the hand against arrow direction. Of particular interest was the finding that reaction performance on both PRO and ANTI conditions was facilitated by congruent and impaired by incongruent flankers. Thus, for both PRO and ANTI conditions motor behaviour was in conformance with the flanker effect on task performance reported in earlier studies (Eriksen and Eriksen, 1974; Eriksen and Schultz, 1979; Gratton et al., 1988; Kopp et al., 1996a, Kopp et al., 1996b).

4.4.1.2. LRP, SAT and P3 latency analyses

LRP profiles and SAT functions indicated that early movement selection on PRO conditions was correct on congruent and incorrect on incongruent flanker trials. On ANTI conditions a reversed activation pattern was found with initial correct hand selection on incongruent and incorrect hand selection on congruent trials. These results show that the hand indicated by pointing direction of the flanker arrows was activated, in line with earlier reports (Coles et al., 1985; Smid et al., 1987; Smid et al., 1990). After flanker based selection, movement of the hand indicated by target arrow direction was prepared. At this time LRP profiles on PRO conditions showed correct motor activation while the LRPs on ANTI conditions indicated incorrect motor activation. In particular the SAT function for incongruent ANTI trials showed a clear dip for motor responses during this period with accuracy levels well below 50% chance. This movement selection based on preliminary information about the target's direction is consistent with the conception that with multidimensional visual stimuli (e.g., composed of color and shape) motor activation can begin as soon as information on a salient stimulus attribute (e.g., shape) becomes available (Smid et al. 1992). Incorrect hand activation on ANTI conditions is finally replaced by activation of the correct hand, against the target arrow, when information on full target identity becomes available. On both PRO and ANTI conditions, final correct LRP asymmetry started earlier on congruent and later on incongruent flanker trials compared with neutral trials. Although for ANTI conditions the latency difference between LRP onsets after congruent and neutral flankers was not statistically significant.

As suggested in earlier studies, the flanker effect on PRO conditions may result from the fact that flanker based motor activations yield an initial motor response benefit

after congruent and an initial response cost after incongruent flankers (Gratton et al., 1988; Smid et al., 1990; Coles et al., 1995; Praamstra et al., 1998). With regard to the influence of preliminary motor activation, the finding of a similar flanker effect on ANTI conditions appears difficult to explain because on these conditions the cost from early motor activation is expected to be highest after congruent stimulus displays. On congruent trials both the flankers and target arrow direction signal the incorrect hand while on neutral and incongruent trials movement errors are induced only by information on target direction. However, the results may still be explained by differences in processing at the motor activation level. Evidence for selection of the hand indicated by arrow direction both after information about the flankers and after partial analysis of the target indicates that subjects adopted a strategy to optimize task performance on PRO conditions. Accordingly, on congruent ANTI trials flanker triggered motor activations may have been considered advantageous and consequently, subsequent activation of the hand indicated by the target's pointing direction may be less strong. In contrast, target direction based movement activation may be stronger after incongruent flankers to compensate for supposed incorrect flanker triggered preparation. Because of these differences in motor response strength, final activation of the correct hand may have been easier after congruent and more difficult after incongruent flankers. It should be noted however that target direction based motor activations cannot have differed much between flanker types. The flanker effects reported were obtained for correct trials only on which incorrect central response activation remained below threshold for peripheral movement execution. Furthermore, incorrect LRP deflections on these correct trials were not significantly different between flanker types. For the delay of final correct hand activation on incongruent ANTI trials there may be alternative explanations. LRP results for this condition show that initial correct flanker triggered hand activations are replaced by opposite hand activation when information on target arrow direction becomes available. During this period the correct hand response channel may be actively suppressed. Consequently, final activation may be delayed if the correct hand channel is not completely released from inhibitory control when activated again after full stimulus information. There also may be a refractory period between successive activations of an error correction mechanism. This mechanism would be active first when flanker based motor activation is substituted by a response of the hand indicated by the target's pointing direction. When stimulus identification is complete the mechanism should act again to enable a response of the hand against target arrow direction. Correct hand activation may be prolonged when the system cannot be addressed a second time within the short latency between identifications of target direction and full target identity.

Although differences at the motor response level, as discussed above, may have contributed, a more straightforward explanation for the present findings is available when assuming that the flanker manipulation differentially affected perceptual processing times. That is, task performance on PRO and ANTI conditions may be facilitated on congruent and impaired on incongruent trials because target recognition time is shorter after congruent and longer after incongruent stimulus displays. Recognition of the central target may take longer on incongruent than on neutral flanker trials when identification of oppositely directed flanker arrows competes with

evaluation of the central target arrow. Conversely, target recognition time may be shorter on congruent than on neutral trials when competition between flanker and target identification also exists to some extent with neutral flankers. However, it also may be that recognition of the target is simply not carried out completely on congruent trials where flankers and target are identical (Eriksen and Schultz, 1979; Hoffman, 1979; Duncan & Humphreys, 1989; Smid et al., 1990; Coles et al., 1995). The conception of differences in perceptual evaluation is supported in particular by the SAT functions on ANTI conditions. These SAT profiles show that compared with neutral trials, the proportion of correct hand activations based on full stimulus information started to increase for earlier reaction time bins on congruent and for later reaction time bins on incongruent trials. A flanker effect on perceptual processing was only partially supported by analysis on peak latency of the P3 component in the ERPs. On PRO conditions, an increase in P3 latency suggested a delay in stimulus evaluation for incongruent stimulus displays, in agreement with previous investigations (Coles et al., 1985; Smid et al., 1990; Praamstra et al., 1998). However, latencies on congruent and neutral flanker trials were not significantly different and, in addition, P3 latency values were comparable for each flanker type on ANTI conditions. It could be that the absence of P3 peak latency differences for these experimental conditions results from the fact that the latency measurements were confounded by overlap of the P3 with preceding ERP negativity N2. Evidence for this comes from the observation that P3 latencies on ANTI trials were similar to latency of the P3 component on incongruent PRO trials (see Table 3 and Fig. 4). Specifically on these conditions also a pronounced N2 was present. Nevertheless, comparable results were obtained when an attempt was made to account for N2 overlap by applying a vector filter procedure in which a frontal-central negative and parietal positive ERP component was modeled (Gratton et al., 1989a; Gratton et al., 1989b).

In summary, the present data indicate that preliminary motor responses were activated based on flanker information and after information about the pointing direction of the central target arrow. On ANTI conditions a flanker effect on reaction performance was found similar to the one observed on PRO conditions. Thus, performance on ANTI conditions also was most optimal when the target was surrounded by congruent flankers, even though in this condition incorrect hand activation was induced both by the flankers and the target arrow's direction. This result suggest that the influence of the flanker manipulation on perceptual processing contributes importantly to the flanker effect on task performance.

4.4.2. Components N2 and P3

Both the N2 and P3 ERP components analyzed in the present study were influenced by the flanker manipulation. Positivity P3 was reduced after congruent flankers on PRO conditions. A similar result was obtained by Kopp et al. (1996a). These investigators suggested that the P3 may be smaller after congruent displays because additional processing to localize and identify the target can be omitted when flankers and target are identical. On ANTI conditions in the present study, P3 amplitude after congruent flankers did not differ from those after neutral and incongruent flankers. This might indicate that subjects continued to full identification of the target on ANTI

conditions, independent of flanker type. However, the P3 components also could be more similar because on ANTI conditions additional processing is required for each flanker type to activate the hand against the target's pointing direction.

On PRO conditions, negativity N2 was clearly evident only in the ERPs after incongruent stimuli. Specifically in this condition, LRP waveform analysis indicated early incorrect central motor activation triggered by the flankers. On ANTI conditions with incongruent flankers a conflict between flanker and target direction based movement selection was present similar to the one observed on incongruent PRO trials. This conflict was followed by a second conflict between target direction based hand selection and final correct opposite hand activation. If each individual response conflict is accompanied by an N2, two subsequent N2 components would be anticipated on incongruent ANTI trials. The first at the same time as the N2 on incongruent PRO trials and the second delayed in accordance with the time between the availability of partial information about the direction of the target arrowhead and complete identification of the target. From the time between incorrect target direction based hand selection and final correct opposite hand activation in the LRPs on ANTI conditions the delay should be about 100 ms. On congruent and neutral ANTI trials only the second conflict between hand activations based on target direction and full target information was present and therefore only the second, delayed, N2 would be expected. The present data indeed showed N2 components for each flanker type on ANTI conditions. However, there was no evidence for two successive N2 components on incongruent trials. In addition, the N2 components for each flanker type on ANTI conditions occurred at the same latency as the N2 on incongruent PRO trials. Therefore, the present findings contradict the presumption that component N2 is elicited with each individual response conflict and accordingly suggest that the N2 cannot be considered a real time correlate of cortical mechanisms associated with incorrect motor suppression.

4.4.3. N2 versus N_e

ERPs on trials with incorrect before correct hand activation showed an additional error negativity N_e compared with ERPs on correct trials. In the stimulus locked ERPs on incongruent PRO and congruent ANTI trials, error negativity appeared at or slightly after the time at which the N2 component occurred on correct trials. Specifically on these conditions early response errors were induced by the flankers. Error negativity was delayed on conditions where response errors occurred later as in particular on ANTI trials with neutral and incongruent flankers. Furthermore, additional negativity in the N2 latency range virtually disappeared for all experimental conditions when trials with early motor response errors were excluded from averaging. Together, these observations indicate that the N_e was time locked more to the incorrect motor response than to the stimulus, in accordance with earlier reports (Falkenstein et al., 1991; Falkenstein et al., 1999; Leuthold and Sommer, 1999). Of special interest was the observation that the N_e occurred after a co-existing N2 component on trials with relatively late response errors. In addition, in line with Falkenstein et al. (1999), the Ne showed a more central topography compared with the N2; amplitude of the N_e was clearly largest at Cz, whereas the N2 showed comparable amplitudes at Fz and Cz. Together, these results supports the hypothesis proposed by Falkenstein and colleagues

that the N_e is functionally different from the N2 (Falkenstein et al., 1999; Falkenstein et al., 2000). As already mentioned, in earlier studies the N_e has been associated with an error detection and/or error inhibition mechanism (Falkenstein et al., 1991; Gehring et al., 1993; Falkenstein et al., 1995; Kopp et al., 1996a; Scheffers et al., 1996). However, in recent work a small N_e like negativity also has been observed after correct motor responses (Falkenstein et al., 2000; Vidal et al., 2000). Related studies suggest that rather than the outcome of a comparison between representations of the actual and required motor response (error detection/inhibition), the N_e may reflect the comparison process itself which is also required on correct trials.

In the response synchronized ERPs on correct trials a single positive component was evident peaking at about 80 ms following motor response onset. In the ERPs on error trials, aligned on incorrect response onset, an initial positive deflection also was observed. However, this developing positivity was abruptly ended due to onset of the N_e. Amplitude of the N_e was larger on ANTI than on PRO conditions, primarily at the Cz lead. The enhancement may relate to the presence of larger incorrect activations on ANTI trials. Both incorrect deflections of the LRP waveforms and EMG of the incorrect hand were more pronounced on ANTI than on PRO conditions and previous investigations have shown that N_e increases with larger response errors (Kopp et al., 1996a; Scheffers et al., 1996; Van 't Ent and Apkarian, 1999). The N_e peaked earlier on congruent than on neutral and incongruent trials and also started earlier on PRO than on ANTI conditions. These results indicate that the N_e was not perfectly time locked to the incorrect motor response. A similar conclusion was derived by Falkenstein and colleagues using choice reaction tasks (Falkenstein et al., 1991; Falkenstein et al., 2000) and Go/NoGo tasks (Falkenstein et al., 1995; Falkenstein et al., 1999). In related studies, stimuli were presented in either the visual or auditory modality. In the recorded ERPs aligned on incorrect motor response onset, component N_e was delayed after auditory stimuli in conditions where both visual and auditory stimuli were potential targets (divided attention) compared with conditions where only the visual or auditory stimuli were designated as target (focussed attention). Assuming that the N_e reflects a comparison between the required and activated movement, Falkenstein and colleagues proposed that with divided attention determination of the required movement was selectively impaired after auditory stimuli due to attention bias in favour of visual stimuli (Hohnsbein et al., 1991). Following this, the results of the present study suggest that identification of the required response was delayed, either when the target stimulus differed from the flankers (i.e., with incongruent and neutral stimulus displays) or when a response of the hand against the target arrow's pointing direction was signaled (ANTI conditions).

4.4.4. Conclusion

Performance of the present flanker reaction task was facilitated by congruent and impaired by incongruent flankers on PRO but also on ANTI conditions. ERPs on PRO conditions showed an N2 component particularly after incongruent stimulus displays. On ANTI conditions an N2 was present for each flanker type, coinciding in time with the N2 on incongruent PRO trials. On incongruent ANTI trials only a single N2 was evident, even though two successive response conflicts occurred in this

condition. Finally, latencies of incorrect motor activations showed a bimodal distribution. Early response errors triggered by the flankers occurred primarily on incongruent PRO and congruent ANTI trials. Later errors occurred for each experimental condition, primarily because subjects anticipated a PRO target while an ANTI target was displayed and also sometimes mistook a PRO for an ANTI target. In the ERPs on trials with early flanker triggered errors, the error negativity N_e occurred at or slightly after the time at which the N2 was evident on correct trials as reported in earlier work (e.g., Falkenstein et al., 2000). However, on trials with late response errors the N_e appeared later and after a co-existing N2 component. Together the present results suggest that the influence of the flanker manipulation on perceptual processing times is a relatively important factor contributing to the flanker effect on reaction performance. The data indicate further that ERP component N2 is not a real time correlate of incorrect motor suppression and provide additional evidence that components N2 and N_e reflect different cortical mechanisms.

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5

Summary and conclusions

In this thesis experiments are described in which electrical brain activity related to the production of voluntary movements and event related potential (ERP) correlates of the regulation and monitoring of actions have been investigated.

In chapter 2 we investigated ERP components and inter-hemispheric amplitude asymmetries of ERPs related to movement preparation and non-motor specific brain functions. Cortical activity was recorded accompanying either finger or saccadic eye movements made in a contingent negative variation (CNV) reaction task. A computer generated pacing stimulus was presented in the left visual hemi-field. The stimulus that resembled a clock provided exact information on the time at which an imperative Go/NoGo signal occurred. The Go/NoGo signal indicated whether a predefined movement should be executed (Go) or withheld (NoGo). Amplitude asymmetries of cortical activity related to movement preparation were examined by means of the lateralized readiness potential (LRP). A measure complementary to the LRP was introduced to extract Non-Motor related Lateralizations (NML).

We found that amplitude versus time profiles of the recorded ERPs were comparable for finger and eye movements. In addition, in line with previous studies (e.g., Bötzel et al., 1993), the LRP for finger movement indicated a build up of contralaterally enhanced cortical negativity with largest asymmetry over the central cortex. In the present CNV task, movement related lateralization of brain potentials preceding ocular saccades was absent. This result contradicts earlier studies that report a dominance of cortical response amplitude over the hemisphere contralateral to saccade direction before self-initiated saccades (Thickbroom and Mastaglia, 1985; Moster and Goldberg, 1990; Klostermann et al., 1994).

However, the NML did indicate a preponderance of non-motor related cortical negativity over the right hemisphere for both movement modalities. Since the CNV stimulus was presented in the left visual field the lateralization, largest over the posterior scalp, presumably reflects the differential activation of primary visual processes. The asymmetry may also relate to directed visuospatial attention, attributed to parietal lobe activity.

The results of our study indicate that lateralization of non-motor function can indeed occur and therefore could have contributed to the previously reported inter-hemispheric asymmetry of brain potentials preceding self-paced saccades. In particular, the asymmetry may represent a covert shift of visuospatial attention toward the saccadic target. Related attention shifts are suppressed in a CNV task where attention is focussed primarily on the CNV stimuli during the pre-saccade period. The absence of saccade related inter-hemispheric ERP asymmetries is regrettable. However, it can also be of good use. For example in reaction task studies concentrating specifically on lateralization of non-motor functions, the use of eye instead of finger movements as response output can be recommended to avoid motor related ERP asymmetries.

The ERP data from the experiment of chapter 2 were also used in the study of chapter 3. In chapter 3, cortical activity after Go and NoGo stimuli was compared to examine ERP correlates of movement inhibition. Because the experimental task was performed with finger and eye movement, the ERP data also allowed us to investigate whether

previously reported Go/NoGo effects on ERP components are specific for hand movement or whether the effects may be generalized across movement modalities.

The recorded ERPs showed that the CNV evident during presentation of the pacing stimulus was terminated by a P300 positivity after the imperative Go/NoGo signal. For both finger and eye movements, the P300 after NoGo stimuli peaked later and was enhanced (primarily at frontal-central scalp sites) compared with the P300 after Go stimuli. In addition, for both movement modalities a similar N2 component superimposed on the positive going limb of the NoGo-P300.

In the ERPs on NoGo trials in which a peripheral motor response was erroneously activated, we also found an N_e error negativity for either movement modality. Analysis of N_e amplitude as a function of error size indicated that the N_e was progressively enhanced on NoGo trials with larger hand or eye movement errors committed.

From this study we conclude that the cortical activity underlying the Go/NoGo differences for ERP components P300 and N2 as well as the cortical mechanism corresponding to the N_e represent general cortical processing associated with suppression and detection of inappropriate motor behaviour, independent of movement output.

In chapter 4 I investigated perceptual and motor related contributions to reaction performance and ERP components after incorrect motor activation in a flanker reaction task. In a flanker reaction paradigm, a target stimulus is presented that signals a movement of the right or left hand. During each stimulus presentation the imperative target is surrounded by distractor elements that are either identical to the target (congruent flankers) or call for an opposite hand response (incongruent flankers). Previous studies consistently found that reaction times were increased after incongruent flankers. The reaction delay has been attributed to a conflict at the motor response level. Final activation of the correct hand indicated by the target may be compromised because it must compete with initial incorrect hand activation triggered by the flankers. However, the reaction delay can also be due to a conflict in perceptual processing. That is, performance may be impaired by incongruent flankers because recognition of the imperative target takes longer when flankers and target are dissimilar.

To examine whether the origin of the flanker effect on reaction performance is mainly located at the motor or at the perceptual level, I measured ERPs, LRPs and reaction performance in a modified flanker paradigm. I used horizontal arrows as targets and congruent or incongruent flankers. A neutral flanker condition, with squares, also was included. In each trial, the fill color of the central target signaled a response of the hand indicated by (PRO condition) or against (ANTI condition) the target arrow's pointing direction. With regard to perceptual processing, I expected to find a replication of the standard flanker effect on reaction performance for both PRO and ANTI conditions. This is because the influence of the flankers on stimulus evaluation time depends on differences in the geometry of the stimulus displays and not on target color. With regard to motor processing I also presumed a standard flanker effect for PRO conditions since in these conditions initial flanker based motor activation is correct on congruent and incorrect on incongruent trials. In contrast, for ANTI conditions the

flanker effect should be reversed because here initial flanker triggered activations are incorrect on congruent and correct on incongruent trials.

The behaviour and LRP results of my study showed that reaction performance was facilitated by congruent and impaired by incongruent flankers on PRO but also on ANTI conditions. The finding of a standard flanker effect for both conditions suggests that the influence of the flankers on perceptual evaluation is a relatively important factor contributing to the flanker effect on task performance.

The experimental data also provided information on the timing of the inhibition related N2 ERP component with respect to incorrect movement selection. In PRO conditions an N2 negativity appeared specifically after incongruent flankers. Only for this flanker type, the LRP indicated a conflict between early incorrect motor activation triggered by the flankers and subsequent correct selection of the hand indicated by the pointing direction of the central target arrow. In ANTI conditions with incongruent flankers the same conflict was evident and followed by a second conflict between selection of the hand indicated by the target's pointing direction and final correct opposite hand activation. Therefore, if each individual response conflict is accompanied by an N2, two subsequent N2 components are anticipated on incongruent ANTI trials. The first component occurring at the same time as the N2 on incongruent PRO trials and the second with a delay corresponding to the time between the moment when partial information about the direction of the target arrow is available and the moment when complete target information is obtained. On congruent and neutral ANTI trials only the second conflict between hand activations based on target direction and full target information was present and accordingly also a single, delayed, N2 was expected for these conditions.

The ERP data did show N2 components after each flanker type on ANTI conditions. However, there was no evidence for two successive N2 components after incongruent flankers and the N2 components for each flanker type peaked at the same time as the N2 on incongruent PRO trials. These findings contradict the assumption that an N2 accompanies each individual response conflict and therefore suggest that the N2 cannot be considered a real time index of a cortical system involved with incorrect movement suppression.

Finally, I also investigated whether ERP component N2 in the ERPs on correct trials and the N_e on trials with reaction errors represent similar (Kopp et al., 1996a; Kopp et al., 1996b) or functionally distinct cortical mechanisms (Falkenstein et al. 1999). Falkenstein et al. (1999) indicated that if their hypothesis that the N2 and N_e correspond to different processes were true, then an N2 should be present also on error trials before an N_e. However, a clear N2 on error trials was not found by these investigators. Falkenstein and co-workers (1999) noted that a possible N2 on error trials may be covered by the leading flank of the N_e.

In my study incorrect hand movement was triggered not only by the flankers but also by incomplete information about the pointing direction of the central target. Especially in ANTI conditions, errors could occur if the hand indicated by the target arrow was activated before information on the combination of target direction and color signaled the correct opposite hand. These target direction based errors start later than flanker triggered errors. Since earlier work has shown that N_e is time-locked closely to

the incorrect motor response, the N_e also should be delayed in the ERPs for trials with these late movement errors. Consequently, overlap of an N2 by the N_e should be reduced. Indeed, in the ERPs on trials with late response errors the N_e occurred later and after a co-existing N2 component. This observation provides further evidence for the conception that the N2 and N_e represent different cortical mechanisms.

The inhibition mechanism assumed to be represented by the N2 ERP component is presumably located in the frontal cortex. In monkeys a formation which appears to be linked to motor suppression has been found in the dorsal bank of the principal sulcus (Sasaki and Gemba, 1986; Sasaki et al., 1989; Gemba and Sasaki, 1990). Dipole source localization studies (Dehaene et al., 1994; Holroyd et al., 1998) and functional magnetic resonance imaging (fMRI) studies (Carter et al., 1998; Kiehl et al., 2000) in humans indicate that the N_e is possibly generated in the anterior cingulate cortex of the medial frontal brain.

6

Samenvatting en conclusies

De interactie van de mens met zijn omgeving komt tot stand doordat de mens zich uit vrije wil kan bewegen en kan reageren op relevante externe gebeurtenissen. Het motorisch gedrag is echter bijna nooit helemaal perfect en daarom is ook een belangrijke taak voor het menselijk informatie systeem weggelegd om de juistheid van gemaakte bewegingen te verifiëren. Op deze manier kunnen responsfouten worden waargenomen en, indien mogelijk, worden gecorrigeerd of tenminste worden beperkt.

In dit proefschrift zijn experimenten beschreven waarin de werking van het menselijk informatie systeem met betrekking tot het maken van vrijwillige bewegingen en de controle en evaluatie van motorische acties worden onderzocht. Hiertoe werd met behulp van het elektro-encefalogram (EEG) de elektrische activiteit van de hersenen gemeten tijdens de produktie en regulatie van motorische handelingen. De experimenten in dit proefschrift concentreren zich primair op de controle van handbewegingen maar ook werd de hersenactiviteit tijdens het maken van oogbewegingen bestudeerd. De manier waarop de sturing van hand- en oogbewegingen is georganiseerd in het brein verschilt sterk. Daarom kan het bestuderen van de hersenactiviteit voor deze twee bewegingsmodaliteiten aanvullende informatie geven op de vraag of de gemeten elektrische potentialen in het EEG specifiek zijn voor bepaalde bewegingen of dat de EEG potentialen gerelateerd zijn aan algemene corticale processen welke actief zijn onafhankelijk van het type beweging wat gemaakt wordt.

In hoofdstuk 2 bestudeerden we componenten in het EEG en verschillen in sterkte van EEG componenten over beide hersenhelften gerelateerd aan de controle van motorische acties en andere, niet motorisch specifieke, functies. De hersenactiviteit werd gemeten tijdens bewegingen gemaakt in een reactietijd test. In het experiment werden in vier onderling gescheiden blokken reacties uitgevoerd met een snelle extensie van de linker wijsvinger, een snelle extensie van de rechter wijsvinger, een snelle oogbeweging naar links of een snelle oogbeweging naar rechts. De visuele reactiestimulus werd door een computer gegenereerd en aangeboden in het linker gezichtsveld van de proefpersonen. De stimulus was een soort analoge klok welke het tijdstip aanduidde waarop een zogenaamd 'Go/NoGo' signaal werd gepresenteerd. Dit Go/NoGo signaal gaf bij elke afzonderlijke stimulus presentatie aan of de voorgedefiniëerde hand- of oogbewegingsreactie daadwerkelijk uitgevoerd diende te worden (Go) of juist niet (NoGo). We onderzochten verschillen in amplitude van het EEG over beide hemisferen veroorzaakt door differentiële activatie van motorische gebieden in de rechter- en linker hersenhelft en verschillen in activatie van centra in beide hersenhelften gerelateerd aan niet-motorische processen.

Een belangrijke bevinding van onze studie was dat de profielen van het gemiddelde EEG tijdens hand- en oogbewegingen vergelijkbaar waren. Met betrekking tot verschillen in motorische activatie vonden we bovendien bij handbewegingen een negatieve EEG potentiaal met grootste amplitude over centraal motorische gebieden in de hersenhelft tegenovergesteld aan de bewegingszijde. Dit resultaat is in overeenstemming met eerdere studies (zie bv., Bötzel et al., 1993) en met het feit dat bewegingen van de linkerhand voornamelijk gecontroleerd wordt door hersencentra in de rechter hersenhelft en vice versa. In onze reactietaak vonden we geen motorisch gerelateerde asymmetrie in het EEG wanneer gereageerd werd met een oog- in plaats

van een handbeweging. Dit resultaat is in tegenspraak met voorgaande studies welke, analoog aan handbewegingen, een negatieve potentiaal vonden met grotere amplitude over de hersenhelft tegenovergesteld aan de richting van de blikbeweging (Thickbroom and Mastaglia, 1985; Moster and Goldberg, 1990; Klostermann et al., 1994). Hierbij dient opgemerkt te worden dat, in tegenstelling tot ons experiment, de oogbewegingen in genoemde studies gemaakt werden op commando van de proefpersoon zelf, niet in reactie op een externe stimulus. De bevinding van een toename in EEG activiteit over de hersenhelft tegengesteld aan de oogbewegingsrichting zou goed in overeenstemming zijn met het feit dat, gelijk aan handbewegingen, de corticale controle van oogbewegingen een contralaterale organisatie vertoont. Elektrische stimulatie van oogbewegingscentra in een hersenhelft resulteert in een beweging van de ogen van de zijde van stimulatie af (stimulatie van de linker hersenhelft: hortizontale oogbeweging naar rechts; stimulatie van de rechter hersenhelft: oogbeweging naar rechts; zie Godoy et al., 1990; Lim et al., 1994).

Wel vonden we bij zowel hand- als oogbewegingen een niet-motorisch specifieke negativiteit in het EEG welke groter in amplitude was over de rechter hersenhelft. Deze inter-hemisferische lateralisatie van het EEG was het sterktst over de achterzijde van het brein en wordt vermoedelijk veroorzaakt door een verschil in activatie van primair visuele hersencentra. Dit omdat de reactiestimulus in het linker gezichtsveld werd aangeboden en het linker visuele gezichtsveld projecteert naar de visuele cortex in de rechter hersenhelft. De asymmetrie kan ook gerelateerd zijn aan een verschil in activatie van corticale processen betrokken bij het richten van de aandacht naar het linker gezichtsveld. De controle van visuele aandacht wordt voornamelijk toegeschreven aan de parietaalkwabben van de hersenen ook achterin het brein, net boven de visuele hersenschors. Analoog aan de primair visuele verwerking wordt de visuele aandacht naar het linker gezichtsveld vooral onderhouden door de rechter parietale cortex.

De resultaten van onze studie geven aan dat inter-hemisferische EEG asymmetrieën als gevolg van verschillen in activatie van niet-motorisch specifieke hersenprocessen inderdaad voor kunnen komen. Deze verschillen in niet-motorische hersenactiviteit kunnen derhalve bijgedragen hebben aan de in eerdere studies gerapporteerde asymmetrie in het EEG voorafgaand aan zelf-geïnitieerde oogbewegingen. De inter-hemisferische lateralisatie in het EEG bij oogbewegingen kan in het bijzonder een gevolg zijn van een verschuiving van het aandachtsveld naar het visuele doel voorafgaand aan de oogbeweging. Een dergelijke verschuiving van het visuele aandachtsveld is onderdrukt in een reactietijd taak waar de aandacht voorafgaand aan de oogbeweging vooral gericht dient te blijven op de centraal gepresenteerde reactiestimulus. De afwezigheid van motorisch specifieke EEG asymmetrieën bij oogbewegingen is op het eerste gezicht betreurenswaardig. Echter deze bevinding kan ook goed van pas komen. Bijvoorbeeld bij reactiestudies met speciale interesse in niet-motorisch gerelateerde EEG asymmetriëen kan de voorkeur gegeven worden om oog- in plaats van handbewegingen als respons te implementeren zodat een bijdrage van verschillen in activatie van motorische hersengebieden aan de gemeten lateralisaties voorkomen wordt.

De meetgegevens van het experiment in hoofdstuk 2 werden ook gebruikt voor het onderzoek van hoofdstuk 3. In hoofdstuk 3 werd het EEG na presentatie van Go en NoGo stimuli vergeleken om hersenactiviteit gerelateerd aan het onderdrukken en detecteren van reactiefouten te onderzoeken.

In eerdere studies gebruik makend van het Go/NoGo paradigma, doorgaans met een handbeweging als respons, zijn twee EEG componenten gevonden welke een toename in amplitude vertonen na NoGo vergeleken met Go stimuli. Dit zijn de N2 (negatieve potentiaal op ongeveer 200 ms na presentatie van de Go/NoGo stimulus) en de P300 (positiviteit op ongeveer 300 ms na de Go/NoGo stimulus). Verder wordt algemeen gevonden dat de P300 na NoGo stimuli een langere latentietijd heeft in vergelijking met de P300 component na Go stimuli. Gezien het feit dat de voorbestemde beweging onderdrukt dient te worden na NoGo stimuli zijn de gevonden N2 en P300 Go/NoGo effecten in verband gebracht met corticale mechanismen betrokken bij motorische inhibitie. Naast deze N2 en P300 Go/NoGo effecten wordt in het EEG na NoGo stimuli waarbij per ongeluk een perifeer motorische respons geactiveerd is ook een extra negatieve potentiaal gerapporteerd. Deze component wordt meestal de 'error negativity' (N_e) genoemd. De N_e is verband gebracht met een frontaal corticaal systeem betrokken bij het detecteren van responsfouten.

Doordat de reactietaak in onze studie was uitgevoerd met zowel hand- als oogbewegingen konden we onderzoeken of de bovengenoemde verschillen in hersenactivatie na Go en NoGo stimuli alsook de N_e bij responsfouten specifiek zijn voor handbewegingen of gegeneraliseerd kunnen worden over bewegingsmodaliteiten.

In ons experiment was in het EEG tijdens presentatie van de klok stimulus een langzame negatieve potentiaal zichtbaar welke na het Go/NoGo signaal werd beëindigd door een P300 positiviteit. We vonden bij zowel hand- als oogbewegingen dat deze P300 component groter in amplitude was en een langere latentietijd had na NoGo vergeleken met Go stimuli. Bovendien was er voor beide bewegingsmodaliteiten na NoGo stimuli een duidelijke N2 component zichtbaar op de positief gaande helling van de P300. Een vergelijkbare N2 was afwezig na Go stimuli. In de hersenactiviteit na NoGo aanbiedingen met responsfouten was ook een N_e 'error negativity' zichtbaar voor beide modaliteiten. De amplitude van de N_e werd groter naarmate de gemaakte hand- of oogbewegingsfout toenam.

Uit deze studie concluderen we dat de hersenactiviteit verantwoordelijk voor de N2 en P300 Go/NoGo verschillen alsmede het corticale mechanisme onderliggend aan de N_e gerelateerd zijn aan algemene hersenfuncties betrokken bij het onderdrukken en detecteren van incorrect bewegingsgedrag, onafhankelijk van de bewegingsmodaliteit.

In hoofdstuk 4 onderzocht ik de relatieve invloed op het reactiegedrag van perceptueel en motorisch gerelateerde verwerkingsprocessen in een flanker reactie experiment. Bovendien werd in deze studie de functionele betekenis van de N2 en N_e EEG componenten, gerelateerd aan respectievelijk het onderdrukken en detecteren van reactiefouten, verder bestudeerd. In een flanker taak wordt een centrale reactiestimulus gepresenteerd welke bij elke afzonderlijke aanbieding aangeeft of de linker- of rechterhand bewogen dient te worden. Bij elke stimulus presentatie worden bovendien direct naast het doel stimulus elementen geplaatst die of identiek zijn aan de centrale

reactiestimulus (congruente flankers) of gelijk zijn aan de reactiestimulus in overeenstemming met een beweging van de andere hand (incongruente flankers). In dergelijke flanker experimenten wordt algemeen een toename in reactietijd gevonden wanneer de reactiestimulus omringd is met incongruente flankers. In eerdere flanker studies is naar voren gebracht dat deze toename veroorzaakt wordt door een conflict op het niveau van motorische preparatie; uiteindelijke activatie van de beweging aangegeven door de reactiestimulus kan bemoeilijkt zijn door een initiële activatie van de incorrecte beweging op basis van flanker informatie. Echter, naast dit motorisch conflict kan de reactietijd toename ook een gevolg zijn van een conflict op perceptueel niveau. Dat wil zeggen, reacties na stimuli met incongruente flankers kunnen bemoeilijkt zijn doordat het herkennen van de centrale reactiestimulus langer duurt wanneer de flanker elementen en de centrale reactiestimulus verschillend zijn.

Om te onderzoeken of het effect van de flankers op het reactiegedrag voornamelijk veroorzaakt wordt door een conflict op motorisch of perceptueel niveau mat ik het reactiegedrag samen met het EEG tijdens reacties in een aangepast flanker experiment. Hierin werden horizontaal gerichte pijlpunten gebruikt als reactiestimuli en congruente en incongruente flankers. Een neutrale flanker conditie met vierkantvormige flanker elementen was ook toegevoegd. Bij elke stimulus presentatie gaf de kleur van de centrale reactiestimulus aan of de hand aangegeven door de aanwijsrichting van de pijl (PRO conditie - pijl naar rechts: rechterhand, pijl naar links: linkerhand) of de hand tegengesteld aan de richting van de pijl (ANTI conditie - pijl naar rechts: linkerhand, pijl naar links: rechterhand) bewogen diende te worden. Aangaande de perceptuele informatieverwerking verwachtte ik een standaard flanker effect te vinden voor zowel PRO als ANTI condities. Dit omdat de invloed van de flankers op de herkenning van de centrale reactiestimulus veroorzaakt wordt door verschillen in vorm van de flankers en de centrale stimulus, niet door verschillen in kleur van de centrale reactiestimulus. Wat betreft motorische activatie verwachtte ik eveneens een standaard flanker effect voor PRO condities omdat voor deze condities de initiële bewegingsactivatie op basis van de flankers correct is na congruente en incorrect is na incongruente flankers. Voor ANTI condities verwachtte ik echter een tegengesteld effect omdat hier de invloed van de flankers op de bewegingsactivatie omgekeerd is met incorrecte activatie na congruente en correct activatie na incongruente flankers.

De gedragsresultaten van mijn studie alsmede het activatiepatroon van centraal motorische hersengebieden evident in de inter-hemisferische amplitude verschillen van het EEG gaven aan dat het reactiegedrag was verbeterd door congruente en verslechterd door incongruente flankers. Dit was het geval voor PRO maar ook voor ANTI condities. Deze vondst van een standaard flanker effect op het reactiegedrag voor beide condities toont aan dat de invloed van de flankers op de perceptuele informatieverwerking een relatief belangrijke rol speelt met betrekking tot het flanker effect op het reactiegedrag.

Uit de experimentele gegevens kon ook aanvullende informatie verkregen worden met betrekking tot de functionele betekenis van de N2 EEG component. Meer specifiek, er kon worden onderzocht of de N2 een real time correlaat is van een inhibitie mechanisme en dus aanwezig is bij elk individueel responsconflict, of dat de N2 alleen verschijnt nadat een motorisch inhibitie mechanisme, één of meerdere malen, actief is geweest. In de PRO condities was alleen een duidelijke N2 aanwezig na incongruente

flankers en ook uitsluitend bij dit flanker type was een conflict aanwezig tussen initiële activatie van de incorrecte hand op basis van flanker informatie en hieropvolgende activatie van de correcte hand aangegeven door de centrale reactiestimulus. Hetzelfde motorisch conflict was aanwezig na incongruente flankers in de ANTI conditie. Hier werd dit conflict ook nog gevolgd door een tweede conflict tussen selectie van de incorrecte hand aangegeven door de richting van de centrale pijl en de hieropvolgende keuze van de correcte hand tegengesteld aan de aanwijsrichting van de centrale pijl. Wanneer elk afzonderlijk motorisch conflict wordt vergezeld door een N2 zijn derhalve twee N2 componenten te verwachten in de ANTI conditie met incongruente flankers. De eerste gelijktijdig met de N2 na incongruente flankers in de PRO conditie en de tweede met een vertraging in overeenstemming met de tijd tussen het moment waarop de richting van de centrale pijl bekend is en het moment waarop volledig informatie over de centrale reactiestimulus beschikbaar is. In ANTI condities met congruente en neutrale flankers is alleen het tweede conflict tussen keuzes van de hand op grond van de richting van de centrale pijl en op grond van volledige informatie over de reactiestimulus aanwezig. Daarom verwachtte ik voor deze condities alleen een enkele verlaatte N2 component.

In het EEG bij de ANTI condities was inderdaad een N2 component aanwezig bij elk flanker type. Er was echter geen bewijs voor twee achtereenvolgende N2 componenten na incongruente flankers en bovendien waren de N2 componenten voor elk flanker type op dezelfde tijd zichtbaar als de N2 in de incongruente PRO conditie. Deze bevindingen zijn in tegenspraak met de veronderstelling dat een N2 component bij elk individueel motorisch conflict aanwezig is en geeft derhalve aan dat de N2 niet gezien kan worden als een real time indicator van een corticaal systeem betrokken bij het onderdrukken van ongepaste motorische acties.

Tenslotte onderzocht ik of de N2 component in het EEG na stimulus aanbiedingen waarop correct gereageerd werd en de N_e na aanbiedingen met initiëel incorrecte hand activatie daadwerkelijk gerelateerd zijn aan funktioneel verschillende corticale mechanismen of mogelijk eenzelfde corticaal systeem vertegenwoordigen. Als een reactiefout gemaakt wordt zal hoogstwaarschijnlijk een poging gedaan worden om de fout te onderdukken. Daarom kan het zijn dat de N_e veroorzaakt wordt door een motorisch inhibitie in plaats van een foutdetectie systeem en dus mogelijk hetzelfde mechanisme vertegenwoordigt als de N2 (Kopp et al., 1996a, 1996b). Als de N2 en N_e daadwerkelijk verschillende processen representeren dan zou in het EEG na reactiefouten ook een N2 aanwezig moeten zijn, voorafgaand aan de N_e (Falkenstein et al., 1999). In eerdere studies is dit echter nooit duidelijk aangetoond. Evenwel dient hierbij de mogelijkheid opgemerkt te worden dat een N2 na reactiefouten niet goed zichtbaar is omdat deze overdekt wordt door de directvolgende N_e component.

In mijn studie werden incorrecte handbewegingen niet alleen gemaakt op basis van flanker informatie maar ook op grond van informatie over de aanwijsrichting van de centraal gepresenteerde pijl. Vooral in de ANTI condities konden reactiefouten gemaakt worden wanneer de hand aangegeven door de centrale pijl bewogen werd voordat informatie over de richting en kleur van de pijl een beweging van de andere hand aangaf. Deze bewegingsfouten beginnen later dan de reactiefouten op grond van flanker informatie. Omdat eerder werk heeft aangetoond dat het moment waarop de N_e zich

voordoet nauw samenhangt met de start van incorrecte bewegingsactivatie is het te verwachten dat de N_e ook later verschijnt in het EEG bij stimulus aanbiedingen met deze late reactiefouten. Als gevolg hiervan zou de overlap tussen de N2 en de N_e verminderd kunnen zijn. In ons experiment bij stimulus aanbiedingen met relatief late reactiefouten verscheen de N_e negativiteit in het EEG inderdaad later en na een coëxisterende N2 component. Deze bevinding geeft aanvullend bewijs voor de theorie dat de N2 en N_e aan verschillende corticale mechanismen gerelateerd zijn.

Het inhibitie mechanisme voor de N2 is waarschijnlijk gesitueerd in de frontale cortex. Bij apen is een formatie gevonden in het dorsale deel van de principale sulcus welke gerelateerd lijkt te zijn aan het onderdrukken van motorische activatie (Sasaki and Gemba, 1986; Sasaki et al., 1989; Gemba and Sasaki, 1990). Uit studies gebruik makend van EEG bron lokalisatie (Dehaene et al., 1994; Holroyd et al., 1998) en functionele Magnetische Resonantie (fMRI) technieken (Carter et al., 1998; Kiehl et al., 2000) bij de mens is gebleken dat de met foutdetectie geassocieerde N_e component vermoedelijk gegenereerd wordt in het voorste deel van de gyrus cinguli in de mediaal-frontale hersenen.

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Curriculum Vitae

Dennis van 't Ent werd op 7 Juli 1967 geboren te Zaandam. In 1983, 1985 en 1987 behaalde hij achtereenvolgens het diploma voor het Middelbaar Algemeen Voortgezet Onderwijs aan scholengemeenschap de Bark en diploma's voor het Hoger Algemeen Voortgezet Onderwijs en Voorbereidend Wetenschappelijk onderwijs aan het Zaanlands Lyceum, allen in Zaandam. In 1993 haalde hij het doctoraal examen in de experimentele natuurkunde, met een aanvullend doctoraal elektronica, aan de Universiteit van Amsterdam. Tijdens de wetenschappelijke stage op de afdeling klinische neurofysiologie van het Academisch Medisch Centrum (AMC) te Amsterdam deed hij onderzoek naar veranderingen in de eigenschappen van saccadische oogbewegingen bij Parkinson patiënten en bij een patiënt met het Parinaud syndroom. Tevens is hij tijdens het laatste jaar van zijn studie part-time in dienst geweest bij het Interuniversitair Oogheelkundig Instituut (IOI) van de Koninklijke Nederlandse Akademie van Wetenschappen (KNAW) te Amsterdam. Tijdens deze aanstelling heeft hij gewerkt aan de analyse van elektrische hersenpotentialen bij de mens opgewekt door middel van visuele stimulatie (Visual Evoked Potentials). Na het doctoraal examen heeft hij van 1994 tot medio 1998 gewerkt aan het huidige proefschrift als Assistent in Opleiding op de afdeling Fysiologie van de faculteit Geneeskunde en Gezondheidswetenschappen aan de Erasmus Universiteit Rotterdam.

Sinds 1 Februari 1999 is hij werkzaam als postdoc onderzoeker bij het centrum voor magneto-encephalografie (MEG) van het Vrije Universiteit Medisch Centrum (VUMC) te Amsterdam.

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