EFFECTS OF DIAZEPAM ON
ATTENTION AND MEMORY:

A PSYCHOPHYSIOLOGICAL AND
NEUROPHYSIOLOGICAL APPROACH
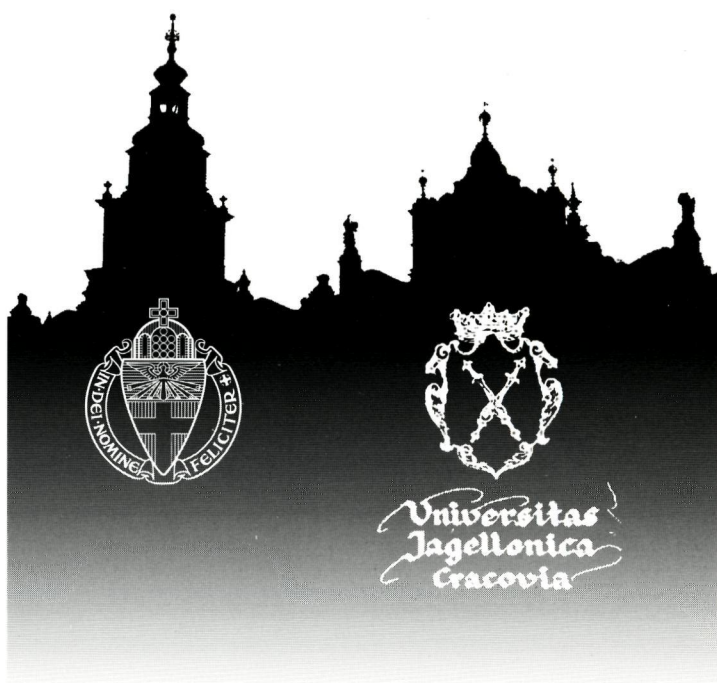
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EFFECTS OF DIAZEPAM ON ATTENTION AND MEMORY: A PSYCHOPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL APPROACH

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dla Mamy i Babci
voor Bob

CHAPTER 1

GENERAL INTRODUCTION

1. Introduction

The central theme of this thesis is an evaluation of diazepam-induced deficits in cognitive processes. More specifically, the experimental work presented in this thesis is devoted to the analysis of attention, memory, motor performance, and the subjective evaluation of the level of vigilance under the influence of diazepam. Two specific questions were investigated in the thesis. The first question was whether the sedative effects of diazepam resulting in a decreased level of vigilance can be held responsible for diazepam-induced amnesia. The second one was whether diazepam-induced memory impairment is related to other disturbances in information processing.

The analysis of effects of diazepam (Valium®) was made in the comparison with another anxiolytic drug - buspirone (Buspar®), which lacks sedative effects that are characteristic for diazepam. The aim of this comparison was to indicate whether the amnestic effects are related to a decreased level of vigilance or to the anxiolytic effects of the drugs. The effects of diazepam on memory were also compared with those of a stimulant drug - methylphenidate (Ritalin®), a drug enhancing the level of vigilance. The aim of this comparison was to evaluate the relationship between the level of vigilance and memory processes. Next, the effects of diazepam on other aspects of information processing were investigated.

Saccadic reaction time (SRT), heart rate (HR) and evoked cardiac response (ECR), event related potentials (ERPs), the performance of memory, attention and concentration, as well as motor performance test and subjective evaluation of vigilance, were used as dependent variables.

1.1. Vigilance

Vigilance can be defined in two ways. Physiologically, vigilance can be specified as a state of the nervous system which makes a speedy and purposeful reaction possible. Behaviourally, vigilance can be described as a performance in observational and inspection tasks. More specifically, vigilance can be considered as the readiness to detect and respond to specific, restricted environmental changes which occur at randomly distributed intervals (Eysenck et al, 1972). A decrement in vigilance gives as result an increase in errors and a

slowing down in the speed of a reaction on stimuli in sustained attention tasks.

Vigilance represents multiple processes. It is influenced by arousal, by expectancy, and by task demands and it describes the overall performance of a task. Vigilance can be modulated by motivational or emotional factors, or by psychoactive drugs (Cohen and O'Donnell, 1993; Hockey et al, 1986). Although there is no homogeneous theoretical background of vigilance, the level of vigilance in general reflects the interaction of the physiological state and the behavioural activity (O'Donnell and Cohen, 1993; Davies, 1983; Hockey et al, 1986; Matejcek, 1982).

Measures of vigilance are of two types (Cohen and O'Donnell, 1993; Hockey et al, 1986). First, the 'tonic' measurement reflects a relatively stable and non-specific measure to any stimulus change. The tonic measurement is less sensitive as an indicator of the momentary variation associated with stimulation. It reflects the general state of vigilance, the base level that determines behavioural responses. Changes of tonic measurement represent long term shifts in baseline vigilance (Cohen and O'Donnell, 1993; Hockey et al, 1986). The second one, the 'phasic' measurement, is considered as the response towards a stimulus or an event. It is a temporal variation associated with stimulation.

1.2. Dependent variables

Vigilance can be subjectively evaluated with the aid of questionnaires and more objectively measured by behavioural performance and physiological variables. Physiological methods comprise tonic and phasic measurements, monitoring non-specific and specific changes to a stimulus. These activities are measured by central and autonomic nervous system variables. There is no unidimentional direction of the physiological pattern at a certain level of vigilance. It is for example possible that blood pressure increases while heart rate decreases during the experimental situation when attention must be paid to the external stimuli (Cohen and O'Donnell, 1993; Davies, 1983; Hockey et al, 1986; Kramer and Spinks, 1991). Therefore, an analysis of more than one physiological variable, especially in combination with performance measurement and subjective reports, can be of value for precise inferences about the effects of changes of level of vigilance on cognitive processes.

Physiological variables, such as saccadic reaction time (SRT), heart rate (HR), evoked cardiac response (ECR) and event related potentials (ERPs), as well as tests applied for measurement of performance (memory, attention and concentration, motor performance) and subjective evaluation, are reported to be valid and sensitive for drug effects (Aman et al, 1984; Ball et al, 1991; Boulenger et al, 1989; Coenen et al, 1989; Ghoneim and Mewaldt, 1990; Korte et al, 1990; Matousek et al, 1984; Risch et al, 1982).

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1.2.1. Subjective evaluation and performance

In order to obtain a subjective evaluation of the level of vigilance, two standard tests concerning subjective alertness were applied. The Thayer test consists of four scales (Thayer, 1986). Each scale describes a different aspect of alertness: the level of general activation, the level of high activation, the level of general deactivation, and the level of deactivation associated with sleep. Each scale is based on five adjectives describing a particular state of vigilance. Subjects are requested to evaluate their subjective state on a four point scale (definitely yes; yes, a little bit; no, rather not; no, definitely not). The Subjective Alertness Scale (SAS) consists of five questions regarding tiredness, sleepiness, arousal, dizziness and speed of reactions (De Sonneville et al, 1984). Subjects are requested to evaluate their subjective state on a four point scale.

Neuropsychological tests used in this study were selected on their sensitivity to drugs effects. Memory, attention, concentration and reaction time tests were used. Memory tests may have an interrelationship and interdependence with attentional processes (O'Donnell and Cohen, 1993). Tests and tasks measuring attention and concentration (Bourdon-Vos test, trail making test, simple reaction time task) and memory (15-word test, 20-word test, paired associated word test, word fluency test, digit span test, complex figure test of Rey and Taylor) were applied (Lezak, 1983; Vos, 1988). Additionally, the effects of the level of vigilance on motor performance (finger tapping task, peg board, simple reaction time task) were evaluated (Lezak, 1983).

1.2.2. Psychophysiological variables
1.2.2.1. Saccadic reaction time

Saccades are fast, short and conjugate eye movements. Functionally, saccades register a new object in the visual field by shifting the eyes from one point to another. Two classes of saccadic parameters are recognised (Findlay et al, 1995; Fischer, 1981; Fischer and Breitmeyer, 1987; Glue, 1991). The first class measures primarily higher central nervous system functions, latency of saccadic eye movements described as saccadic reaction time (SRT). The second class provides information of the performance of the structures that generate saccades. This class includes measures of saccades duration, peak velocity, accuracy of saccades and peak acceleration and deceleration. These are determined by the autonomic nervous system (Fischer and Breitmeyer, 1987; Glue, 1991). Once initiated, saccadic eye movements are automatic and can not be modified by practice or voluntary effort and are not under cognitive control (Fischer and Breitmeyer, 1987; Glue, 1991).

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Saccadic eye movements are generally studied when the eyes are fixated and a saccadic eye movement is made to a target stimulus. Within the paradigm, two conditions can be related to the offset of the fixation point. In the 'gap' paradigm the offset of the fixation point occurs before, while in the 'overlap' paradigm the offset occurs after the onset of the target stimulus. The difference in SRT between gap and overlap conditions opens the possibility to investigate whether an assumed underlying process, the 'disengagement of attention' (Posner, 1980), is influenced by a change in vigilance.

The SRT is related to cognitive processes, for the reason that the SRT indicates the time to make a decision about the saccade target and to decide whether or not a saccade will be produced. Any changes in the attentional system require a certain time which is included in the SRT. The SRT varies, for example, with the overlap paradigm upon instructions to pay attention to the fixation point or to ignore it (Fischer and Breitmeyer, 1987; Mayfrank et al, 1986; Posner, 1980; Posner et al, 1987).

1.2.2.2. Heart rate and evoked cardiac responses

It is long known that the level of vigilance influences the tonic heart rate (HR) and this is mediated by the autonomic nervous system. An inverse relation between the level of vigilance and the tonic HR is described, tonic HR is increased with a lower level of vigilance (Barry and Tremayne, 1987; Barry, 1996). Also the phasic activities of the heart (evoked cardiac response, ECR) are psychologically important. Both tonic and phasic types of activities can be studied during information processing tasks (Barry and Tremayne, 1987; Cohen and O'Donnell, 1993).

The ECR is proposed as a non-invasive measure of cortically mediated effects of an event on autonomic control of the heart (Barry, 1982; Lacey and Lacey, 1978). It is considered as an index of attentional allocation; it depends on when passive sensory intake or active effort processing is required (Cohen and O'Donnell, 1993).

The ECR is biphasic and consists of the sum of two independent response components: an initial HR deceleration (ECR1) and a subsequent HR acceleration (ECR2) (Barry, 1984; Barry and Tremayne, 1987). The cardiac deceleration is considered as an index of stimulus registration and is independent of stimulus parameters (Barry, 1983). The HR acceleration is interpreted as an index of mental processes. It reflects the evaluation of the stimulus and it might be considered as an index of cognitive load. The degree of cardiac acceleration is a function of task difficulties and efforts necessary to accomplish a task (Barry, 1982; Barry, 1988).

1.2.2.3. Electroencephalogram and event related potentials

There are two types of bioelectrical brain activity measurements (Cohen and O'Donnell, 1993; Hockey et al, 1986). The spontaneous electroencephalographic activity (EEG) is considered a tonic measurement, while the event related brain potentials (ERPs) are seen in terms of phasic measurements. The tonic measurement is measured by a spectral analysis of a certain duration sample of spontaneous EEG. For example, a fast Fourier transformation procedure can be used. Such a procedure produces a power spectrum, which quantifies the contribution of an array of sine waves of different frequencies to a complex waveform (Cohen and O'Donnell, 1993). Spontaneous EEG activity shows changes in frequency due to changes in the level of vigilance. Different psychological states are associated with different frequency waveforms. Alert attentiveness is characterised by a mainly desynchronised, fast frequency, low amplitude beta waves; relaxed wakefulness is characterised by alpha waves. During sleepiness and light sleep spindle bursts, large slow waves and a loss of alpha waves is observed (Matejcek, 1982).

The phasic measurement, the event related potentials (ERPs), indicates small changes within the EEG, due to the occurrence of external or internal events. In order to extract the time-dependent ERPs from the ongoing EEG, EEG responses on repeated stimulation are averaged. ERPs waveforms are described in terms of components of negative and positive waves. The components of ERPs are functionally categorized into two types: exogenous and endogenous (Coles et al, 1990). The exogenous components of short latencies (less than 100 msec after stimulus onset), are considered as a response to the physical properties of the stimulus and are not influenced by task demands. The endogenous components, occurring after 100 msec after stimulus onset, are related to mental processes and vary according to psychological factors, such as task relevance, expectancy and stimulus probability (Cohen and O'Donnell, 1993; Coles et al, 1990; Van der Molen et al, 1991).

The P300 component is a long-latency endogenous component of the ERP. Its maximum amplitude peak occurs between 250 and 500 msec. The polarity of P300 is always positive and reaches its maximum at Pz. P300 is elicited with an 'oddball paradigm'. This consists in its simplest form of the presentation of two types of stimuli which differ in the probability of occurrence; respectively, targets in 20% of cases and standards in 80% of cases. The P300 is considered as the response to targets. The P300 component has been extensively evaluated since it was reported by Sutton et al in 1965 (Cohen and O'Donnell, 1993). Various authors claim that there are not a single but there are various factors underlying this component. The P300 is dependent on probability, stimulus quality, attention, task relevance, cognitive demands, decisive and context updating processes or motor responses (Cohen and O'Donnell,

1993; Duncan-Johnson and Donchin, 1982; Johnson, 1986; Pritchard, 1981; Verleger, 1988). Characteristics of the P300 component provide strong evidence that this component is evoked by cognitive processes, stimulus evaluation, and mental load manipulated by instructions (Cohen and O'Donnel, 1993; Donchin and Coles, 1988; Duncan-Johnson and Donchin, 1982; Johnson, 1986; Pritchard, 1981).

Squires et al (1975) evaluated the component following the P300 and labelled it 'slow wave' (SW). The SW is, similar to the P300 component, evoked by targets in the oddball paradigm. The amplitude of the SW depends on the localisation and changes along the midline (negativity at Fz and positivity at Pz). It has been suggested that SW reflects further cognitive processes beyond those reflected by P300, indicating a final stage of evaluation of the trial, showing additional processing of this stimulus (Ruchkin et al, 1980a; Ruchkin et al, 1980b; Ruchkin et al, 1988; Squires et al, 1975). Moreover, these authors also indicate a relation between P300 and SW and suggest an opposite change in amplitude of these components when accuracy in responding or reaction time is modulated.

1.3. Psychoactive drugs

Manipulation of the level of vigilance was done by the administration of tranquillizers and stimulant drugs. In order to obtain a decrease or an increase in vigilance, diazepam (Valium®), a representative of the class of benzodiazepines, and a stimulant, methylphenidate (Ritalin®), related to the amphetamines, were administered. Moreover, a second anxiolytic drug without sedative effects, buspirone (Buspar®) (Goldberg and Finnerty, 1982; Riblet et al, 1982; Rickels et al, 1982), was applied in order to investigate whether the anxiolytic action or the decrease in the level of vigilance was responsible for putative cognitive deteriorations.

1.3.1. Diazepam

Benzodiazepines were discovered in the USA by Leo Sternbach, a chemist of Polish-Jewish origin (Sternbach, 1980). Sternbach's experimental work, that led to the discovery of the benzodiazepines, began with the synthesis of a class of substances which he had already examined before World War II at the Jagiellonian University in Cracow, Poland. With this discovery the extended work began on this class of psychoactive drugs, which led in 1957 to the development of the first benzodiazepine, chlordiazepoxide (Librium®). This drug was approved for therapeutical use in humans in 1960. Diazepam was synthesised by Sternbach in 1959. This is a benzodiazepine which is characterised by a significantly greater effectiveness than chloordiazepoxide. Diazepam was introduced on the market in 1963 as Valium®.

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Benzodiazepines are applied as anxiolytic, hypnotic, muscle relaxant, and antiepileptic drugs (Lader, 1980; Speth et al, 1980). They also can be used as premedication for anaesthesia to minimise presurgical anxiety. In spite of their efficacy and safety, benzodiazepines induce several side-effects (Lader, 1980). The most common one is sedation, which is associated with feelings of fatigue, drowsiness and inattention. Furthermore, memory impairments and deteriorations of psychomotor performance are reported (Ghoneim et al, 1984a; Ghoneim et al, 1984b). Benzodiazepines potentiate actions of alcohol (Lader, 1980). In addition, tolerance, dependence and withdrawal syndromes are also reported (Lader, 1980). Finally, muscle relaxation which might disturb motor-coordination is also considered as an unwanted effect (Beaumont, 1988; Lader, 1980; Hinrichs and Ghoneim, 1987).

A continuous balance of excitatory and inhibitory systems exists in the brain. A change in this balance in the direction of too much activation is the biological substrate for phenomena such as anxiety, sleeplessness and epileptic attacks. Although the precise mechanism of action of benzodiazepines is still not completely understood, it is known that benzodiazepines inhibit excitations and activations. This results in anxiolytic, sleep-inducing, anticonvulsant and muscle relaxant effects. The action of the benzodiazepines is provided through a specific benzodiazepine-GABA-chloride ionophore receptor complex in the brain discovered by Braestrup and Squires (1977) and by Möhler and Okada (1977).

These receptor complexes are distributed in different densities across the entire brain. The occurrence of the benzodiazepine-GABA-chloride ionophore receptor in the brain indicates the existence of natural substances which also fit to these receptors and potentiates the main inhibitory neurotransmitter gamma-amino-butyric acid (GABA). This action is imitated by benzodiazepines, which are thus considered as agonists at GABA receptors. It is thought that benzodiazepines modulate the shape of the GABA receptor complex. This is done in such a way that GABA better fits on this receptor and opens the chloride channels more widely, which induces an increase of the inhibitory action. Such a mechanism is called allosteric modulation (Moleman, 1982).

1.3.2. Buspirone

Buspirone is a non-benzodiazepine tranquillizer which possesses anxiolytic properties comparable to those of the benzodiazepines. Buspirone, an azaspirodecanedione compound, was synthesised by Wu and Rayburn at Bristol Myers in the early 1970s. Originally, buspirone was maintained as an antipsychotic agent in schizophrenic patients. Although buspirone was almost ineffective in those patients, anxiolytic properties were discovered. Initial studies in psychoneurotic patients with primary diagnosis of anxiety neurosis showed buspirone to be as

effective as diazepam, but without the characteristic side-effects for benzodiazepines (Goldberg and Finnerty, 1982; Levine, 1988). In 1986, buspirone (Buspar®) was approved for the treatment of anxiety (Tunnicliff, 1991).

Buspirone reduces anxiety without causing impairments of psychomotor and cognitive functions. Sedation, the main side-effect of benzodiazepines, is only reported in about 10% of patients treated with buspirone, which incidence is comparable to that of the placebo effect (Seidel et al, 1985). On the contrary, it is even suggested that buspirone may have slight stimulating effects (Goa and Ward, 1986; Schuckit, 1984). Moskowitz and Smiley (1982) describe that driving skills tend to improve after buspirone intake. Moreover, opposite to benzodiazepines, buspirone has no anticonvulsant and muscle-relaxant properties and is not effective as a hypnotic. Moreover, buspirone does not induce tolerance, dependence, or withdrawal syndroms. Buspirone also does not potentiate alcohol actions (Goa and Ward, 1986; Lader, 1988; Napoliello and Domantay, 1988). Buspirone, however, cannot be considered an ideal drug. The physical symptoms as dizziness, headache, restlessness and nervousness, light-headeness, insomnia, and excitement are reported as buspirone's side-effects (Eison and Temple, 1986; Levine, 1988). Furthermore, in circumstances where immediate relief of anxiety is required, for example in acute stressful situations, buspirone may not be useful due to its slow onset of action. On the contrary, a lack of dependence potential in combination with its slow action may be an indication for applying buspirone in situations inducing more persistent or chronic anxiety. Therefore, buspirone seems to be the best remedy for anxiety associated with prolonged stress, for patients with anxious personality, and for pathological anxiety states (Beaumont, 1988).

Buspirone is unrelated to the benzodiazepines (Eison and Temple, 1986; Peroutka, 1985; Tunnicliff, 1991). The exact action of buspirone is still not clearly established, despite the fact that buspirone interacts with several different neurotransmitter systems. The serotonergic activity is suppressed while the dopaminergic and noradrenergic systems are enhanced. The most important effect of buspirone is related to its activity at a newly defined subset of 5-hydroxytryptamine (5-HT), serotonergic receptors, called the 5-HT_{1A} receptor. Buspirone is a 5-HT_{1A} partial agonist at these presynaptic receptors and inhibits serotonergic transmission (Peroutka, 1985; Tunnicliff, 1991).

1.3.3. Methylphenidate

This stimulant belongs to the large amphetamine family. Methylphenidate was synthesised in 1944 by Penzion as a cyclised derivative of amphetamine. The synthesis was replicated by Mier in 1954. Originally, methylphenidate (Ritalin®) was introduced on the

market by Ciba-Geigy as a new geriatric medication in the early sixties. Its chemical similarity to the amphetamines suggested its use in the treatment of children with behavioural disorders (Greenhill, 1991). Stimulants are in general used in order to prevent or suppress state of exhaustion and feelings of tiredness which might occur after exertion, during long and monotonous activity, or following sleep deprivation. Stimulants are also used in order to prevent the 'attacks' of sleep in narcoleptic patients and suppress the appetite in the treatment of obesity as a diet pill (Levine, 1990).

Therapeutically, stimulants, especially methylphenidate, are most commonly prescribed for the treatment of children's hyperactive syndrome. The 'attentional deficit hyperactivity disorder' (ADHD) is characterised by inattentiveness, motor unrest, learning disorders, and impulsivity (Diener, 1991). The paradoxical calming effects of this type of drugs are considered the result of an increase of alertness and goal directed concentration leading to a reduction of the restless-impulsive behaviour and hyperactivity. Thus, an improvement of the level of vigilance, an increase of the accuracy of performance, and an increased speed of reaction time, especially in a vigilance task, are commonly reported as the effects of methylphenidate intake.

The effects of a single dose of a stimulant of the amphetamine family are manifested by an increased level of vigilance, attentiveness, and wakefulness. A single dose of these drugs elevates mood, often providing euphoria (Levine, 1990). The unwanted side-effects of methylphenidate are similar to these of amphetamines, but they are less frequent and savage in comparison with amphetamine (Spiegel, 1990). The most common side-effects are insomnia and sleep disturbances, suppressed appetite under the condition that methylphenidate is not prescribed to decrease it, and nervousness. Furthermore, the frequent use of methylphenidate might lead to tolerance, dependence, and withdrawal syndromes (Diener, 1991; Shaywitz and Shaywitz, 1991).

Methylphenidate is an indirectly acting sympathomimetic amine in the pheripheral adrenergic system. It mimics the effects of noradrenaline by displacing it from the peripheral adrenergic nerve endings. The drug appears to act similarly in the brain where it has been shown to release both noradrenaline and dopamine by displacing these neurotransmitters from the vesicles, enhancing their release. Methylphenidate is also a potent inhibitor of the uptake of these neurotransmitters and this inhibition tends to enhance and prolong its effects (Iversen and Inversen, 1981).

1.4. Experiments

The main aim of the thesis is to investigate the influence of drug induced changes in vigilance on behavioural and cognitive processes. The level of vigilance is manipulated by the

administration of psychoactive drugs which decrease or increase vigilance. In the first experiment described in Chapter 2, the effects of benzodiazepines, inducing a decrement in vigilance, are established on attentional processes. More specifically it is questioned to which extent, vigilance changes induced by diazepam affect the process of disengagement of attention. The effects of diazepam are studied on saccadic eye movement, in a 'gap' as well as in an 'overlap' paradigm. Next, the effects of benzodiazepines on tonic heart rate and on an evoked cardiac response were investigated in a stimulus evaluation task (Chapter 3). In particular, the influence of diazepam on two aspects of stimulus significance (attention and signal value) was analysed. In Chapter 4, the effects of benzodiazepines on cognitive processes expressed in the P300 and slow wave activity were investigated. This was done with the aid of two comparisons. In the first comparison a classical oddball task is used. In the second comparison the event related potentials (ERPs) of a neutral stimulus are compared with the ERPs of an identical stimulus, but now presented under increased cognitive load. In Chapter 5, another, drug-free, ERPs experiment is presented in which task demands were varied in different ways in order to investigate the relationship between the various types of late positivities. This was done in order to facilitate the interpretation of the drug induced changes in ERPs. In Chapter 6, the effects of benzodiazepines, inducing a decrement in vigilance, are established on memory processes. It is additionally questioned whether the sedative effect of diazepam can be held responsible for the amnestic effects that are commonly found after intake of benzodiazepines. For this purpose two anxiolytics, diazepam with sedative effects and buspirone without sedative effects, are compared. In Chapter 7 it is investigated whether an opposite manipulation, an increase in vigilance, as studied in Chapter 6, will indicate the relation between vigilance and memory. The stimulant methylphenidate is used to increase the level of vigilance.

CHAPTER 2

EFFECTS OF DIAZEPAM AND BUSPIRONE ON REACTION TIME OF SACCADIC EYE MOVEMENTS[1]

Abstract - Effects of the anxiolytic drugs diazepam and buspirone were studied on the reaction time of saccadic eye movement. The study was performed with 8 healthy volunteers in a double-blind, placebo-controlled way. The purpose was to investigate the putative drug effects on the first step of an attention shifting process: the disengagement of attention. Saccadic reaction time was measured in two conditions: the 'gap' and the 'overlap' condition. In the first condition a delay is present between the offset of the fixation spot and the onset of a target, while in the second condition the offset of the spot is overlapped by the onset of the target. Clear differences in saccadic reaction time in the expected direction were found between the two conditions, with longer reaction times of saccadic eye movements in the overlap condition. The nonsedative anxiolytic buspirone in a dose of 5 mg had no significant effects on saccadic reaction times, while clear effects of diazepam in a dose of 5 mg were established. Diazepam slowed down saccadic reaction times, reduced the number of fast saccades and facilitated the number of slow saccades. However, the effects induced by this drug were identical for the two conditions. The latter result implies that the disengagement of attention is not selectively disrupted by diazepam. Perhaps the action of diazepam is expressed in other attention factors, such as in shifting attention or in the reengagement of attention. A slowing down of these processes by the vigilance-lowering properties of diazepam might be the cause of the prolonged latencies. The increased latencies of saccadic eye movements induced by a low dose of diazepam may have practical implications.

2. Introduction

Saccadic eye movements are the most rapid movements that the oculomotor system is capable to produce. Saccadic movements allow subjects to switch their eyes quickly from one point of interest to another in order to register new objects in the visual field (Bittencourt et al, 1981). In general, the saccadic eye movement system is studied by tracking a small spot, while the position of the head is fixed. Subjects are instructed to focus on a particular point, then a target is presented and a saccadic eye movement follows. Based on the saccadic reaction time (SRT), saccades can be subdivided into four main categories, namely: (1) 'slow regular' saccades with a reaction time larger than 190 msec; (2) 'fast regular' saccades with a reaction time of 140-190 msec; (3) 'express' saccades with a reaction time of 80-140 msec, and (4)

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'anticipatory' saccades, with a reaction time shorter than 80 msec. The latter saccades occur when the direction of the target is predictable (Fischer, 1981; Fischer, 1986; Fischer and Ramsperger, 1984; Fischer and Breitmeyer, 1987; Fischer and Weber, 1993; Kalesnykas and Hallet, 1987).

Voluntary saccadic eye movements are influenced by attentional processes (Braun and Breitmeyer, 1988; Fischer, 1986; Fischer and Weber, 1993; Remington, 1980). In terms of the theory of Posner (Posner, 1980) and Posnet et al (1987), the SRT is dependent on a shifting process in attention. Three mental operations can be distinguished in this process (1) the ability to disengage attention from its current focus, the fixation point; (2) the ability to shift the attention to a new location, the target point, and (3) the ability to engage attention to this new spot. Before the onset of a saccade takes place there is the process of releasing the target. Then the eyes are moved to a new target and attention is engaged to this new target (Fafrowicz et al, 1993; Fischer, 1981; Fischer, 1986; Fischer and Breitmeyer, 1987; Mayfrank et al, 1986; Reulen, 1984).

Two different paradigms are commonly used in these studies: the 'gap' and the 'overlap' paradigm. In the 'gap' paradigm the fixation point is extinguished before the onset of the target and a temporal delay is introduced between the offset of the fixation point and the onset of the target. The SRT is then generally about 120-150 msec. In the 'overlap' paradigm the fixation point is presented until the onset of the target or it even overlaps the onset of the target. Then, the SRT is about 250 msec (Becker and Fuchs, 1969; Fischer, 1981; Zambarbiery et al, 1982). By comparing the results obtained by the 'gap' and the 'overlap' condition, the first of the three mental processes postulated by Posner (1980) and Posner et al (1987) can be studied: the disengagement of attention. In the 'gap' condition this process occurs before the onset of the target, whereas it immediately occurs after the appearance of the target in the overlap condition. The longer SRTs in the 'overlap' condition are the manifestation of this disengagement process (Becker and Fuchs, 1969; Fischer 1986; Zambarbiery et al, 1982). SRTs are reproducible within subjects, both between tests and within test periods (Ball et al, 1991; Mercer et al, 1990). Learning effects only occur after days of daily practice with large numbers of saccades (Fischer, 1981). Saccades are sensitive for the effects of psychoactive drugs (Ball et al, 1991; Glue, 1991; Griffiths et al, 1984). Diazepam (Valium®), a classical representative of the benzodiazepines which are acting as GABA agonists, is commonly prescribed for its anxiolytic effects as well as for its hypnotic, muscle relaxant, and antiepileptic actions. Despite its efficacy and safety, diazepam produces adverse cognitive effects such as sedation expressed in decreased alertness and vigilance, and memory impairments (Boulenger et al, 1989; Ghoneim et al, 1984a). Buspirone (Buspar®) is a relatively new anxiolytic which does not belong to the family of the benzodiazepines and mainly acts as a serotonin agonist

(Tunnicliff, 1991). It is currently used in disorders related to anxiety. Buspirone lacks the hypnotic and sedative properties of benzodiazepines. It does not influence vigilance while the memory impairments and changes in motor performance are minimal (De Maio, 1988; Goldberg and Finnerty, 1982; Schuckit, 1984; Unrug et al, 1992). The aim of the present experiment is to establish and compare the influence of the two anxiolytic drugs diazepam and buspirone on the disengagement of attention, measured by differences in SRT in the 'gap' and the 'overlap' conditions. It is hypothesised that diazepam with its hypnotic and sedative actions might affect more selectively the disengagement of attention, for the reason that this process demands more control than the automatic process of shifting the attention or the reengagement of attention does. This could mean that diazepam might more specifically enhance SRTs in the 'overlap' condition. It is also hypothesised that the effects of buspirone might be smaller, due to a lack of hypnotic and sedative action.

2.1. Methods and Materials
2.1.1. Subjects and Design

Five female and three male volunteers aged between 25 and 31 years served as subjects. All subjects had normal vision acuity, did not use any medication, and were healthy. All agreed to participation and signed an informed consent. Subjects had to refrain from alcohol the day before the experiment. On the morning of the experimental day, they were allowed to have a low-fat containing breakfast, whereby tea and coffee were not permitted. Each subject participated in three sessions which occurred at intervals of minimally 1 week. In this within-subject design, subjects received either 5 mg diazepam, 5 mg buspirone or placebo in a counterbalanced sequence. The buspirone and the placebo group consisted of 8 subjects, but for technical reasons the data from 2 subjects from the diazepam group had to be rejected. So 6 orders of drug administration were identical in each group.

2.1.2. Procedure

Drugs were administered orally in a double-blind way and administration was followed by a break of half an hour. After that time, subjects remained in a dimly lit and sound-isolated room and were seated in an easy chair, having the head position stabilised by a chin rest. A computer screen was situated 60 cm ahead from the subjects. They were asked to perform two types of visual, horizontal tracking tasks, one in the gap and one in the overlap paradigm. The order of the two tasks was counterbalanced over subjects and drugs. Since the experimental days were separated for at least 1 week and saccadic eye movements are stable between

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sessions, order and crossover effects were assumed to be absent, which was confirmed statistically. A complete session lasted about 50 min and each paradigm took about 25 min. In the overlap paradigm, subjects were asked to attend and to fix a point in the center of the screen. The target point was randomly displayed 5 or 10 degrees to the right or left of the fixation point. The target point was always turned on for 2 seconds after the onset of the fixation point. Subjects were asked to make a target-directed saccade in response to the target's onset as quickly as possible. The sequence of fixation and target point was repeated 10 times per minute. The gap condition task was almost similar to the 'overlap' condition and the only difference was that a delay of 200 msec was introduced between the offset of the fixation point and the onset of the target. The 200 msec gap is effective in producing saccades with latencies below 140 msec (Mayfrank et al, 1986).

The eye movement registration system Ober2-duo was used. Using an infrared corneal reflection recording technique with a resolution of 5 min of arc and an accuracy of 10 ms, this system measures on-line horizontal eye movements. SRTs were measured by an IBM/AT computer with a millisecond counter that was started at the onset of the target and stopped at the beginning of the saccade. Subjects wore occulographic goggles. A five-factor repeated measures analysis was carried out on the mean SRTs, with subjects as a 'between-group' factor and paradigm (2 levels), drug (3 levels), direction (2 levels) and degree (2 levels) as 'within-group' factors. There were no main effects for degree and direction and no simple interactions between these factors. Therefore, the latter two factors were excluded from further statistical analysis and the data were pooled. It should be acknowledged that not all fourth- and fifth-order interactions could be statistically evaluated, considering the number of subjects and factors in the design.

2.1.3. Statistical Evaluation

To determine whether saccades were differentially influenced by the drugs, they were divided into the four earlier mentioned categories: 'anticipatory', 'express', 'fast regular' and 'slow regular' saccades. A four-factor repeated measure analyses was performed on the number of saccades, with subject as a 'between-group' factor, and paradigm, drug (3 levels), and type of saccade (4 levels) as 'within-group' factors. Perhaps due to the sedative action of diazepam fewer saccades appeared in the diazepam condition. Compared to placebo there were 10% less saccades in the 'gap' condition and 17% less in the 'overlap' condition. Therefore, the percentage of the number of saccades was used to allow a straightforward comparison and arcsinus transformation on the number of saccades was considered to be appropriate, since the values were sometimes close to zero (Winer, 1971). Transformed data, however, did not yield

other differences than untransformed data.

2.2. Results

Table 1 Means and SDs of SRTs in milliseconds under the 'gap' and the 'overlap' paradigm in the placebo, the buspirone and the diazepam group.

Paradigm	Placebo	Buspirone	Diazepam
Gap	155.3 ± 22.3	152.7 ± 26.4	167.8 ± 36.6
Overlap	191.0 ± 19.0	208.8 ± 30.8	217.0 ± 24.0

Mean SRTs for the 'gap' and the 'overlap' condition in the three drug groups are presented in Table 1. Main effects of the condition (F=39.11, df=1,7, p<0.0001) and the drugs were detected (F=5.97, df=2,12, p<0.01). SRTs were shorter in the 'gap' condition and the post-hoc test according to Scheffé showed that the SRTs were prolonged after intake of diazepam compared to placebo (p<0.05). The interaction between drug and condition, especially expected for diazepam, was not significant.

Table 2 Mean percentages with SEMs of four types of saccades under the gap and the overlap paradigm for the placebo, the buspirone and the diazepam group.

Saccades	Placebo	Buspirone	Diazepam
Gap			
Anticipatory	3.7 ± 1.2	3.0 ± 0.9	2.2 ± 1.3
Express	53.5 ± 9.2	50.8 ± 10.2	34.8 ± 9.3
Fast regular	31.4 ± 5.8	30.0 ± 5.9	41.0 ± 4.7
Slow regular	11.5 ± 5.0	16.3 ± 6.3	22.0 ± 9.5
Overlap			
Anticipatory	0.0 ± 0.0	0.2 ± 0.1	0.0 ± 0.0
Express	11.4 ± 4.7	7.6 ± 4.0	5.2 ± 3.5
Fast regular	49.6 ± 4.8	43.7 ± 6.4	34.7 ± 5.8
Slow regular	39.0 ± 6.1	48.6 ± 8.5	60.1 ± 7.0

The results on the number of saccades are presented in Table 2. There was a main effect for the numbers, transformed into percentages, of the four types of saccades (F=11.61, df=3,21, p<0.0001), indicating that there were substantial differences in the percentage of the various types of saccades. In general, there were only a few 'anticipatory' saccades, while the

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'fast regular' saccades occurred most often, followed by the 'slow regular' saccades and the 'express' saccades. There was also a significant paradigm by type of saccade interaction ($F=16.67$, $df=3,21$, $p<0.0001$). Scheffé's post-hoc tests showed that there were more 'fast regular' and more 'slow regular' and less 'express' saccades in the 'overlap' condition, compared to the 'gap' condition. Finally, there was also a drug-by-type saccade interaction ($F=5.18$, $df=6,36$, $p<0.001$). This interaction points towards the fact that the drugs differentially influenced certain types of saccades. Diazepam facilitated a shift towards a higher number of slow saccades, at the cost of the other types of saccades. Neither the drug-by-paradigm interaction not the second-order interaction appeared to be significant.

2.3. Discussion

Clear differences in mean SRTs were found for the 'gap' and 'overlap' condition. SRTs were longer in the 'overlap' condition, which was in agreement with expectations. There were also less 'fast regular' and 'slow regular' and more 'express' saccades in the 'gap' condition. This was most clear in the placebo group. In general, these differences are in concordance with earlier work in our (Fafrowicz et al, 1993) and other laboratories (Fischer, 1981; Fischer, 1986; Weber et al, 1993). Diazepam prolonged SRTs in the gap as well as in the overlap condition and facilitated the percentage of slow saccades. This effect is not due to the commonly noticed deteriorations in the speed of motor performance (e.g. Unrug et al, 1992), since the latency of the movement is used as the dependent variable and not the velocity or the duration of the saccade itself. The latency is determined by the first sign of an eye movement reaction. The main outcome is that diazepam had the same effects in both the 'gap' and the 'overlap' condition and that there were no drug-by-paradigm interactions for the SRTs, nor for the percentages of the four types of saccades. This implies that the influence of diazepam was the same for both conditions. These results shed some light on whether the disengagement of attention in the shifting process is influenced by drugs. Since both drugs do not differentiate between 'gap' and 'overlap' conditions and since the disengagement process was present, as expressed in longer SRTs in the overlap condition, it is concluded that the disengagement of attention is not selectively disrupted by the two drugs. The SRT enhancement after diazepam intake is probably affected by a general slowing down of central processes such as the organisation of the execution of a saccade, or, in terms of Posner (Posner, 1980) and Posner et al (1987), by a slowing down of the shift in attention or the reengagement of attention at the target. This general slowing down of attention processes can also be found after intake of diazepam in reaction time tasks in which reaction and movement time are separated (Sakol and Power, 1988).

Other authors have also studied the effects of benzodiazepines on saccadic eye

movements and have concluded that saccadic eye movements are especially altered by drugs active at the GABA/benzodiazepine receptor complex (Glue, 1991; Hikosaka and Wurtz, 1985a; Hikosaka and Wurtz, 1985b). Generally, velocity and duration of saccades were found to be changed by benzodiazepines. The increase in SRT, however, is not always found (Ball et al, 1991; Rothenberg and Selkoe, 1981), although an increase in the saccadic latency has been reported for flunitrazepam (Hofferberth, 1986), as well as for diazepam (Roy-Byrne et al, 1993). The reason for this discrepancy is still not quite clear.

Although the working mechanism of buspirone is not completely clarified, it is suggested that it binds to serotonin receptors (Tunnicliff, 1991). Compared to benzodiazepines, little is known about the effects of the serotonin agonists on saccadic eye movements. There are only some indications in the involvement of serotonergic pathways in the control of saccades (Eison and Eison, 1984). The clinical efficacy of buspirone against anxiety is comparable to the benzodiazepines and the nonanxiolytic effects of these two drugs must also be considered. The clear effects of diazepam and the lack of changes of buspirone must be viewed against this background. It is generally accepted that buspirone has fewer adverse effects on brain processes than the benzodiazepines have. Earlier we have found that the effects of diazepam and buspirone on memory, as well as on attention, concentration, psychomotor performance and subjective feelings were different. In all cases almost no changes after buspirone intake were found. It is suggested that the commonly reported cognitive deterioration of diazepam is due to its hypnotic and sedative actions (Unrug et al, 1992), which is in line with others (Boulenger et al, 1989; Ghoneim et al, 1984a; De Maio, 1988, Goldberg and Finnerty, 1982; Schuckit, 1984; Sakol and Power, 1988). In short, it is proposed here that the effects of diazepam on saccadic eye movements are due to its sedative and hypnotic properties. Under normal circumstances, saccades are made when a change in the visual field is observed. Prolonged latencies might have a practical consequence: the ability for subjects to respond to a change in the visual field is reduced. This is probably more true under a high load of stimulus presentation, in which situation not all changes can be registered. Additionally, the blurred vision occasionally described as an adverse effect of benzodiazepines may play a role (Brand et al, 1974). From that viewpoint, we suggest that diazepam-treated subjects may miss more peripheral visual events, especially under a high stimulus load. This may have implications for everyday life.

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INFLUENCE OF DIAZEPAM AND BUSPIRONE ON HUMAN HEART RATE AND THE EVOKED CARDIAC RESPONSE UNDER VARYING COGNITIVE LOAD[2]

Abstract - The influence of two anxiolytics on basal heart rate and on the evoked cardiac response elicited by auditory stimuli was studied in humans. Diazepam (Valium®) (7.5 mg) and buspirone (Buspar®) (7.5 mg), which differ in their psycho-pharmacological profiles, were used. Prestimulus vigilance and cognitive load were manipulated by instructions allowing the subjects to ignore the stimuli, or requiring them to count the tones. Drug effects were obtained in subjective alertness, basal heart rate level, and the evoked cardiac response. Diazepam reduced subjective alertness while buspirone did not. Diazepam apparently increased heart rate levels relative to placebo, in contrast to buspirone which produced an apparent decrease in heart rate. These drug-induced prestimulus heart rate level effects were associated with differential decelerations immediately following stimulus onset and appear to reflect differences in prestimulus vigilance. Opposite effects of the drugs were also observed in the second, acceleratory, component of the evoked cardiac response, and these were found to be independent of the prestimulus drug effects. Compared with placebo, buspirone appeared to enhance the acceleratory component in the count condition, while diazepam led to an apparent reduction of this component. Enhancement of this acceleration component after buspirone may reflect an increase in cognitive effort directed to the performance of task-relevant behaviour, while the reduction of this component after diazepam can be regarded as a cognitive-motivational neutralisation of signal value. The differential effects of the two anxiolytics support the separation of the evoked cardiac response into different components and have implications for the clinical use of the drugs.

3. Introduction

The human evoked cardiac response (ECR) elicited by an innocuous stimulus is essentially a biphasic response. When minimal task requirements are imposed upon the subject, a simple deceleration in heart rate (HR) occurs: ECR1. With an increase in stimulus significance, produced by the instruction to cognitively respond to the stimulus in some way (e.g. to count the occurrences of the stimulus), there is an additional relatively large acceleration in HR following, and sometimes obscuring, the initial deceleration. That is, the biphasic ECR consists of an initial deceleratory ECR1 followed by an acceleration (ECR2) in those situations

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Figure 1 Evoked cardiac responses under NEUTRAL and COUNT conditions. The NEUTRAL response is taken as ECR1, the first component of the evoked cardiac response. ECR2 is a hypothetical component which adds to ECR1 to produce the biphasic response observed under COUNT conditions. The emphasised parts of the curves indicate non-overlapping portions which contain ECR1 and ECR2 maxima.

Change in HR (BPM)

Time relative to stimulus onset (sec)
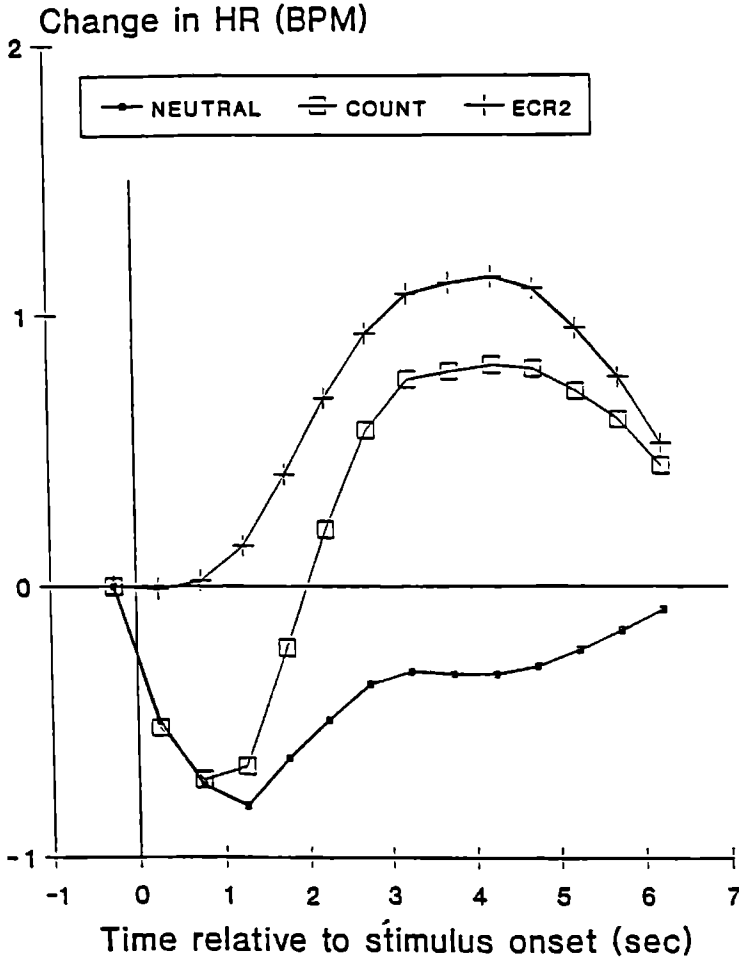
ECR1 observed under minimal task requirements, (ECR1 + ECR2) observed under cognitive load, and the hypothetical ECR2 component generated as the difference between the two observed responses.

The initial HR deceleration (ECR1) is identifiable as a primary bradycardia (Barry, 1983). Lacey and Lacey (1980) have shown that brief stimuli prolongate the cardiac cycle in which the stimulus onset occurs, and also the subsequent cardiac cycle. After these two slower heart beats, a return towards the base line occurs. This reflex bradycardia was considered by Lacey and Lacey (1980) as a correlate of an 'early process of stimulus registration'. The accelerative component (ECR2), which is markedly affected by variations in cognitive load (e.g. Barry, 1988), thus may be treated as a correlate of an experimentally defined set of mental processes (Kaiser et al, 1993). Hence, the biphasic ECR may be described as the sum of two relatively independent response components (ECR1 + ECR 2), and these may be separated by appropriate experimental manipulations (e.g. Barry and Tremayne, 1987). Note that ECR2 does not occur alone (since ECR1 is a mandatory reflex response to stimulus onset), and that some form of subtraction of responses elicited in different conditions is required for its estimation.

A simple manipulation of situational demand, such as increasing the significance of the stimulus by instructions, may have two separate effects on the ECR: enhancement of the initial poststimulus HR deceleration and the generation of a subsequent HR acceleration. These two effects are related to two aspects of stimulus significance: attention and signal value. Attention is associated with prestimulus vigilance and may also have preparatory effects apparent in shifts in HR level. In contrast, the signal value associated with a stimulus is definable in terms of what the subject does after the stimulus onset, e.g. silently counting the stimulus occurrence (Barry, 1982), and is thus an index of cognitive load.

The experiment to be described examined the changing of HR levels and the shape of the phasic evoked cardiac response to stimuli of varying significance under the influence of two types of anxiolytic drugs: diazepam, a well-known member of the benzodiazepine family, and buspirone, a new anxiolytic drug chemically and pharmacologically unrelated to the benzodiazepines (Riblet et al, 1982). Benzodiazepines are GABA-agonists and known for their sedative and amnestic effects (Ghoneim and Mewaldt, 1990), while buspirone does not belong to this class of drugs but is regarded as a serotonergic agonist (Tunnicliff, 1991). It does not have sedatory and amnestic actions (Seidel et al, 1985; Unrug et al, 1992). Diazepam and buspirone are considered to have equivalent anxiolytic properties at doses in the 5-20 mg range (Boulenger et al, 1989; Schuckit, 1984; Seidel et al, 1985). The time course of plasma values of diazepam and buspirone are also similar, with both reaching a peak within 90 minutes after oral administration (Boulenger et al, 1989).

We report a study which used stimulus significance and drug as independent variables.

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Both prestimulus and poststimulus cardiac activity, corrected for respiratory sinus arrhythmia, were treated as the dependent variables. The significance of the stimulus was defined, prior to its repeated presentation, by instructions that the subject should silently count the stimuli (COUNT) or that there was no task involving the stimuli (NEUTRAL). Both conditions were used with each subject under the influence of diazepam, buspirone, and placebo in order to examine the impact of the differential amnestic and sedative drug effects on cardiac functioning in this theoretical context. In the COUNT condition the instruction may involve some increasing of attention in preparation for an expected series of stimuli and prepares the subject's performance of appropriate mental activities immediately following stimulus presentation. The COUNT instruction allows us to study the two components of stimulus significance. According to the earlier considerations the first component is identifiable as vigilance, a preparatory attentional focusing prior to stimulus onset associated with changes in both prestimulus HR levels and the phasic ECR1, while the second component is identifiable as signal value (cognitive load) and is associated with HR acceleration (ECR2). The hypothesis is that diazepam and buspirone will differentially modulate the form of both prestimulus and poststimulus aspects of cardiac activity in the context of variation in stimulus significance. Because of its sedative effect diazepam is expected to reduce vigilance, thus increasing prestimulus HR levels and reducing ECR1 compared with buspirone. If the sedative effect also interferes with effortful cognitive processing, ECR2 will be relatively reduced by diazepam. The anxiolytic effects of the drugs on these cardiac measures are unknown.

3.1. Methods

Twelve volunteers aged 20-28 years served as subjects and were paid Dfl. 30,- for three experimental sessions. Participants did not report the use of any medication, and were declaredhealthy. They were all aware that psychoactive drugs were to be examined. All signed an informed consent form as part of the protocol approved by the University of Nijmegen.

Heart rate and respiration were recorded from the same 10 mm diameter Ag/AgCl ECG electrodes connected to an S&W ECG and respiration device. Electrodes were fixed to the chest in a triangle, one left, one right and one above the heart, just under the neck. The output from an R-wave peak detector was used to compute R-R intervals.

Each subject participated in three sessions. The experiment was carried out in a double blind fashion. The day before each session of the experiment, subjects had to refrain from alcohol. On the morning of each experimental day they were allowed to have only a low-fat breakfast, tea and coffee were not permitted. Each subject received diazepam (Valium®) in a dose of 7.5 mg, buspirone (Buspar®) also in a dose of 7.5 mg, or placebo, in separate

sessions, 1 week apart, in a semi-random order, in which each drug appeared equally often at each position. Drugs were administered orally. Drug administration was followed by a 45 min. break prior to recording. Recording lasted 30 min. Subjects were seated in a comfortable armchair in an air-conditioned, electrically-shielded, sound-isolated chamber separate from the recording equipment. The subjects received two sets of 10 innocuous auditory stimuli (60 dB, 1000 Hz, 1 sec duration, 20 msec rise/fall times), with interstimulus intervals randomly varying between 40 and 60 sec. Stimuli were presented in each of two conditions, defined by instructions that there was no task involving the stimuli (NEUTRAL), or by instructions to silently count the tones (COUNT). The order of presentation of conditions was counterbalanced between subjects in each session. At the end of the session subjective alertness was measured by a Subjective Alertness Scale.

Measures of cardiac activity were calculated in terms of mean values of HR at 0.5 sec intervals for 30 sec epochs commencing 20 sec before each stimulus. Corresponding values of respiratory activity were obtained and used in trial-by-trial off-line analyses to remove the effects of respiratory sinus arrhythmia from the HR values (Barry et al, 1993; Barry and Wortmann, 1994). This iterative regression procedure does not change the form of the averaged cardiac response profile (pre or poststimulus), but reduces between-trial variability caused by respiration. Removal of cardiac 'noise' due to respiratory sinus arrhythmia clarifies both prestimulus and poststimulus aspects of cardiac responding.

3.2. Results

The data concerning the Subjective Alertness Scale showed a significant difference between the placebo (mean 18.5, SD 2.3) and diazepam group (mean 15.2, SD 2.6) $F(1,11)=7.82$, $p<.01$. There were no differences between placebo and buspirone (mean 16.5, SD 2.1).

The averaged cardiac response profiles after removal of respiratory sinus arrhythmia are shown in Figure 1 and were discussed above in relation to the separation of the ECR1 and ECR2 components. These data are averaged across subjects and drugs, but separated for the NEUTRAL and COUNT conditions. Corresponding profiles as a function of drug condition are shown in Figure 2.

3.2.1. Prestimulus HR levels

It appears from Figure 2 that, relative to placebo, buspirone produced a reduction in HR

Figure 2 The raw data underlying Figure 1 separated by drug. Note the differences in prestimulus heart rate (HR) levels as a function of drug.
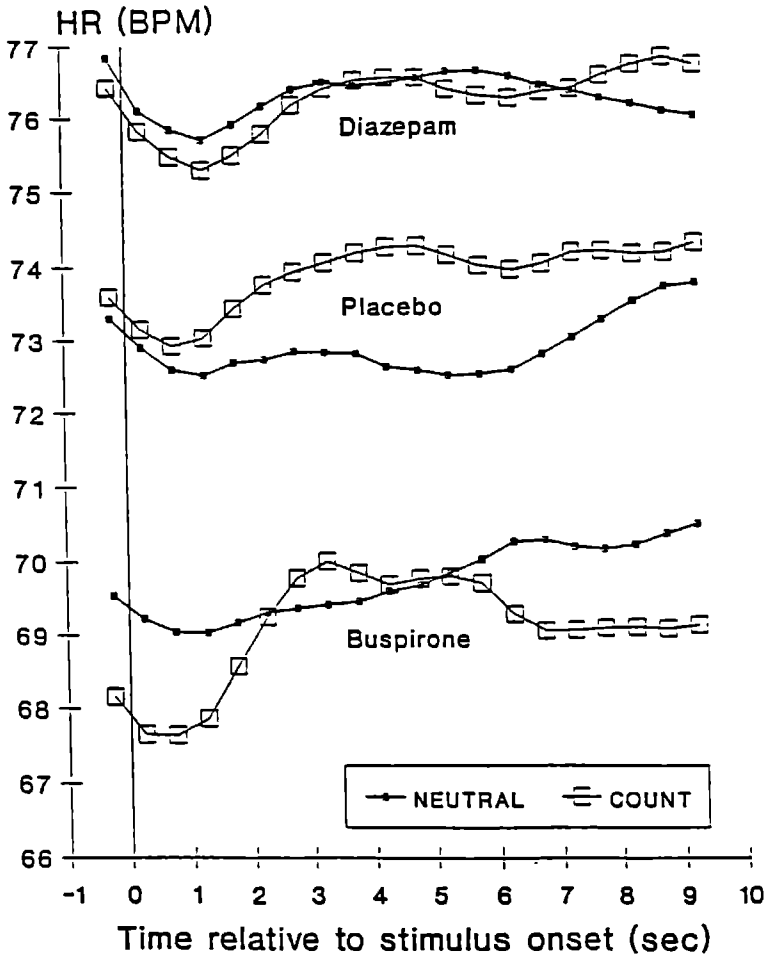
level immediately prior to stimulus onset of approximately 4 beats per minute (BPM), while diazepam produced an almost similar increase in HR level.

These data were submitted to a two-way repeated measures ANOVA with within-subject factors of DRUG and INSTRUCTION (COUNT versus NEUTRAL). Within the DRUG factor, orthogonal planned contrasts compared the effects of buspirone with diazepam, and their average with placebo. Such orthogonal planned contrasts provide maximum sensitivity in detecting statistical differences and were used in preference to more-direct but less sensitive post-hoc tests because of the relatively small N. A significance level of $p<.05$ was adopted throughout.

The prestimulus mean found with buspirone (68.83 BPM) was significantly lower than that associated with diazepam (76.45 BPM), $F(1,11) = 5.41$, MSe = 129.07. There was no difference between the average of these (72.64 BPM) and that found with the placebo (73.23 BPM), $F<1$. These two results together suggest that buspirone decreased HR below the normal activity level associated with placebo, while diazepam increased HR levels. There was no effect of INSTRUCTION ($F<1$) and no interactions between the DRUG contrasts and INSTRUCTION ($Fs<1$). That is, no instructional effects approached significance in the prestimulus levels.

3.2.2.   ECR components

In the relative biphasic responses following stimulus presentation, as shown by the change scores in Figure 3, in comparison with the response profile associated with placebo, diazepam appears to have produced a larger ECR1 component, while buspirone appears to have produced an increased ECR2 component.

3.2.2.1.   ECR1

In order to link with previous work on ECR1/ECR2 separation, deceleratory ECR1 effects were investigated using simple trend analyses over the 7 data points in the interval from the immediately-prestimulus level to 3 sec poststimulus onset. This is the portion of the data marked by the heavy line on the NEUTRAL response in Figure 1. It can be seen that this covers the peak of the averaged ECR1 component. Data were submitted to a three-way repeated-measures ANOVA using TIME (7 data points), DRUG and INSTRUCTION as within-subject factors. Within TIME, the quadratic trend was examined. Within DRUG and INSTRUCTION, the same planned contrasts as described for the prestimulus levels analysis were employed. These effects all involve single degree of freedom F tests, and hence avoid the problems of non-

Figure 3 Phasic responses relative to prestimulus levels for each condition and drug. Note the different effects of drug apparent in the ECR1 and ECR2 components.
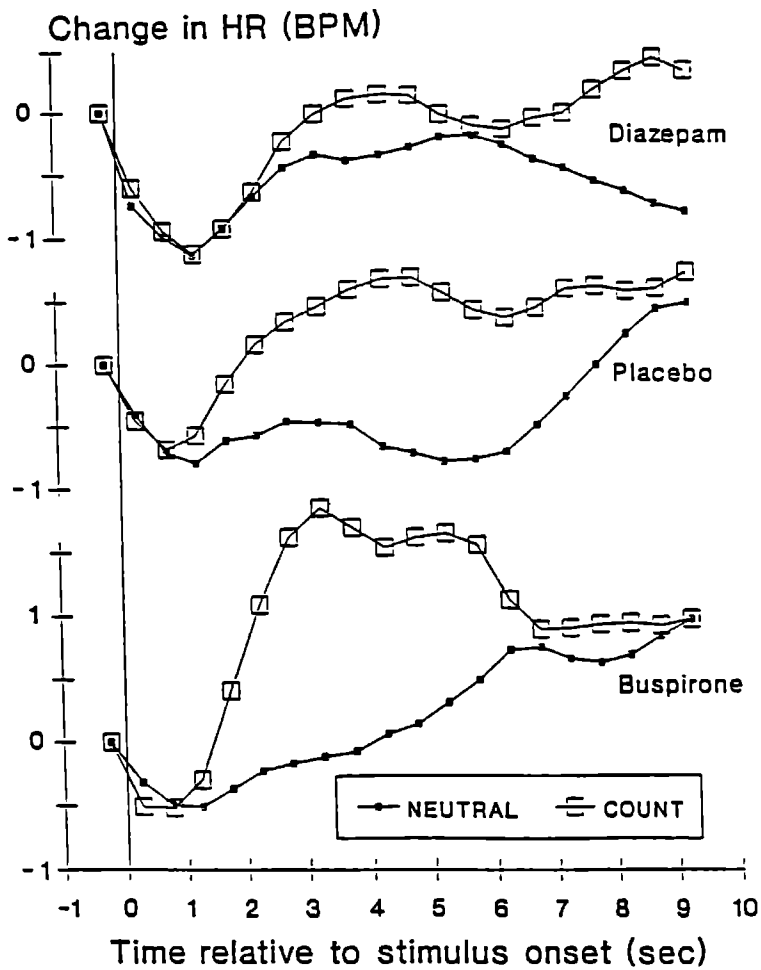
sphericity often encountered in repeated-measures designs with autonomic data. ECR1 was apparent as a significant quadratic trend over time (F = 47.77, MSe = 0.86). This represented a significant deceleration over the period, F = 8.61, MSe = 6.98. There was a main effect of DRUG associated with the larger response with diazepam compared with buspirone (F = 4.95, MSe = 7.15), but the average of these responses did not differ from that associated with placebo (F<1). Overall, these results suggest that the deceleratory ECR1 was relatively enhanced by diazepam, and relatively reduced by buspirone, in comparison with the drug-free response observed in the placebo condition.

3.2.2.2. ECR2

The acceleratory ECR2 was estimated in terms of the quadratic trend over time-points in a corresponding window commencing 2.5 sec after stimulus onset. This is indicated by the heavy line in the derived ECR2 curve of Figure 1, and can be seen to capture the peak response. A similar factorial ANOVA was used. The acceleratory response form was reflected in a significant quadratic trend over the time points in this window, F = 6.79, MSe = 1.00. The accelerative component represented by ECR2 was larger in the COUNT than in the NEUTRAL condition, reflected in a significantly different quadratic trend, F = 6.37, MSe = 0.28.

This also contributed to a mean difference in cardiac acceleration in this window which approached significance, F = 3.34, MSe = 31.82, p = .09. Although the response form did not differ as a function of drug, the overall acceleration produced by buspirone was significantly larger than that produced by diazepam, F = 7.35, MSe = 11.27. Overall, these results indicate that ECR2 was, as expected, more apparent in the COUNT compared with the NEUTRAL condition, and suggest that buspirone produced an enhancement in ECR2, while diazepam produced a reduction in ECR2, relative to that which occurred under placebo conditions.

3.2.3. Role of prestimulus changes in ECR1 and ECR2 effects

The role of the drug-produced prestimulus shift in HR level in determining these ECR1 and ECR2 drug effects was investigated using analyses of covariance. Measures of ECR1 and ECR2 amplitude were obtained by averaging the deviations from the immediately-prestimulus level within each window used in the previous trend analyses. Separate two-factor (DRUG and INSTRUCTION) repeated-measures analyses were carried out for ECR1 and ECR2, with the corresponding values of prestimulus HR as covariates.

The planned contrasts over drugs used previously were included in the analyses. This allows direct comparison of the drug effects in the response component amplitudes with and

without consideration of the covariate effect. For the amplitude of ECR1, the F value for the comparison of diazepam with buspirone was reduced from 4.95 to 1.85, a non-significant value. That is, the previously-noted difference in ECR1 as a function of drug is attributable to the change in prestimulus HR levels under the different drugs. For the amplitude of ECR2, although the F value for the comparison of diazepam with buspirone was reduced from 7.35 to 6.54, it still remained statistically significant. That is, the drug effect in ECR2 was not significantly mediated by the drug effect in the prestimulus HR level.

3.3.   Discussion

In general, as measured by the Subjective Alertness Scale, diazepam decreased vigilance and induced sedation, while buspirone did not exert such effects.

A significant differential drug effect was obtained in basal HR level. Diazepam was associated with higher HR than buspirone was. The finding that average HR under drug conditions did not differ from placebo thus implies that diazepam increased HR while buspirone decreased HR. The effects are not large enough for these implications to be confirmed statistically in our sample.

The apparent enhancement of HR level under the influence of diazepam is compatible with the results obtained by Korte et al (1990), who reported that diazepam caused an increase in the mean HR of rats. The authors suggested that diazepam might have acted directly on the cardiovascular regulatory mechanism. From other sources it is known that benzodiazepines generally increase HR in man (DiMicco, 1987; Libert et al, 1988). Under the influence of buspirone, HR level here was apparently decreased in relation to placebo. This result would contradict previously-reported findings that buspirone does not influence HR level (Goa and Ward, 1986; Tyrer et al, 1985), and requires further investigation. These changes in HR level reflect an apparently opposite influence of the two drugs on the nervous system.

There were corresponding drug effects in reported vigilance (decrease with diazepam) and prestimulus HR (apparent increase with diazepam). These are consistent with the view that diazepam causes a centrally-mediated reduction in vigilance. It should be noted, however, that there were no instructional effects upon the prestimulus HR level. This failure to link the expected instructional vigilance effect with prestimulus HR changes may have resulted from the relatively low level of vigilance required in this study since the stimuli were all well above threshold. In principle however, it could weaken the centrally-mediated vigilance interpretation of the diazepam effects, suggesting that this mechanism should be explored further in future studies.

The poststimulus HR data obtained in this study showed a general biphasic response to

the stimulus. According to the studies outlined in the Introduction, the initial deceleration is a correlate of an early stimulus registration process, while the following acceleration is a correlate of mental performance, being larger in the COUNT condition. The data concerning drug influence on the form of the phasic ECR showed clear differential effects on the two response components. The larger deceleration component (ECR1) obtained under the influence of diazepam and the decreased ECR1 component associated with buspirone were not confirmed as independent effects in the analysis of covariance. We consider that these differences in ECR1 reflect the differential prestimulus drug effects in HR level.

The apparent enhancement of the acceleration component (ECR2) under the influence of buspirone may reflect a facilitation effect in the mechanisms involved in cognitive processing. From the Laceys' perspective, cardiac acceleration results in baroreceptor effects which reduce the efficiency of the cortical areas associated with the processing of external stimuli, thus differentially facilitating internal processing or cognition. Diazepam appeared to impair these mechanisms. These data agree with the reported differential effects of diazepam and buspirone on memory and psychomotor performance (Unrug et al, 1992).

According to Barry (1982) the acceleration component of the ECR is a physiological correlate of the subject's mental performance due to an instructionally-defined signal value, and this was verified here. The apparent enhancement of this acceleration component after buspirone may reflect an increasing of mental concentration on the task, associated with higher energy channelled to the performance of a particular kind of task-relevant behaviour. In contrast, the apparent diazepam effect (reduced ECR2) can be regarded as a cognitive-motivational neutralisation of signal value. Thus, the two kinds of anxiolytic drugs appear to interfere with the instruction 'Count the stimuli' in opposite ways. Commonly, it is found that benzodiazepines induce anterograde amnesia (Ghoneim and Mewaldt, 1990). The underlying mechanism of this amnestic effect, however, remains unclear although various suggestions can be found that reduced vigilance and attention leads to less stimulus elaboration and subsequent shallower consolidation. In line with this, the present results suggest that the instructionally defined signal value is decreased under the influence of diazepam.

It can be concluded that diazepam and buspirone, at a dosage of 7.5 mg, show clear but opposite effects on HR level, as well as on the separable components of the phasic ECR. Diazepam is associated with an enhancement of prestimulus HR level and the initial deceleratory ECR component. In contrast, under the influence of buspirone, HR level and the initial deceleratory ECR component decrease. The differential effects in ECR1 were shown to be mediated by the drug-induced prestimulus HR effects and are not considered as reflecting differential drug effect upon stimulus registration. The ECR2 effects suggests that diazepam produces relative impairment of post-registration cognitive processing, while this aspect of task

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performance in the context of signal value seems to be enhanced by buspirone. The differential drug effects confirm the independence of these two cardiac response components and their underlying mechanism (Barry and Tremayne, 1987).

In this study buspirone appears to have enhanced both prestimulus vigilance and poststimulus cognitive processing required in the task, relative to placebo. These effects may reflect the anxiolytic aspect of the drug allowing enhanced attention in the laboratory task. The possibility of such an enhancement is deserving of future research effort.

These differential cognitive processing effects may have clinical implications, particularly in the context of the anxiolytic properties of the two drugs being equivalent. It may be occupationally disadvantageous for some patients to have the task-relevant aspects of their cognitive processing impaired which, as we suggest, happens with diazepam. For such patients, buspirone may be the preferred medication. Although consonant with established psychopharmacological differences, this suggestion is supported by our interpretation of the psychophysiological data from a relatively limited study and should be reassessed in the light of future behavioural studies. However, our data suggest potentially fruitful directions for such behavioural research, and indicate the importance of the inclusion of psychophysiological perspective in that effort.

CHAPTER 4

EVENT RELATED POTENTIALS IN A PASSIVE AND AN ACTIVE AUDITORY CONDITION: EFFECTS OF DIAZEPAM AND BUSPIRONE ON SLOW WAVE POSITIVITY[3]

Abstract - The effects of single, oral doses of diazepam (10 mg), buspirone (10 mg) and placebo on auditory event related potentials were assessed in healthy volunteers. Subjects received two series of auditory stimuli: a series of identical stimuli presented in a neutral, passive condition and a series of identical standard tones (p=.8), but now intermixed with target tones (p=.2), in an active, oddball condition. The analysis focused on the average value of the potential in two different phases, from 250 till 574 msec post-stimulus (including P300) and from 576 till 900 msec post-stimulus (including late slow wave positivity). Event-related potentials for the standards of the oddball task were compared with the potentials of the same stimuli presented in the neutral condition. In addition, the classical comparison between the target and the standard in the oddball task was made. The first comparison was designed to isolate any effect of a change in the level of vigilance and attention due to involvement in the oddball task. This effect was evident as an increase in positivity that was smaller in the diazepam condition. The second comparison was designed to isolate the distinctive processing associated with task-relevant stimuli. This revealed that the P300 was reduced in the 250-574 msec window in the diazepam group. Both results suggest that cognitive processing of relevant stimuli is reduced by diazepam. Presumably, this is associated with the sedative effects of this drug. Consistent with this interpretation, subjects under the influence of diazepam made more omissions in the detection of targets in the oddball condition and had longer reaction times. In contrast to diazepam, the anxiolytic buspirone did not appear to have measurable effects on cognition.

4. Introduction

Benzodiazepines are of great importance for the treatment of anxiety and insomnia. In spite of their efficacy and safety, they also produce adverse effects such as decreases in vigilance, disorders in psychomotor functions, and impairments in memory functions (Coenen et al, 1989; Ghoneim and Mewaldt, 1990; Gorissen et al, 1995; Taylor and Tinklenberg, 1987; Unrug et al, 1992). A second type of an anxiolytic drug, currently used in anxiety-related disorders, is the serotonergic agonist buspirone. Buspirone is free of the hypnotic and sedative properties associated with a decrease in vigilance, and some investigators have suggested that it does not influence memory functions (Boulenger et al, 1989; De Maio, 1988; Goldberg and

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Finnerty, 1982; Riblet et al, 1982; Taylor and Tinklenberg, 1987; Unrug et al, 1992).

The objective of this study is to investigate the differential effects of diazepam, an anxiolytic of the classic benzodiazepine group, and buspirone, a non-sedative anxiolytic, on cognitive processes expressed in components of event related potentials (ERPs). Previous studies have shown that ERPs are sensitive to psychoactive drugs. These drugs induce characteristic changes on components of ERPs (Bartel et al, 1988; Bond et al, 1983; Böker and Heinze, 1984; Ebe et al, 1969; Erwin et al, 1986; Herrmann et al, 1981; Martin et al, 1992; Nichols and Martin, 1993). In the present study, two conditions were used: a passive, neutral condition and an active, oddball condition. In the neutral condition subjects were told just to listen to a series of identical stimuli (no response was required). In this condition, emphasis is laid on the physical, intrinsic properties of the stimuli. In the oddball condition, subjects were required to discriminate between target stimuli and standard stimuli; the latter were identical to the tones presented in the neutral condition. In this condition, aspects of responding and properties extrinsic to the stimulus, such as intention or instruction, are engaged (Shiga, 1977). Subjects were instructed to press a button after the detection of a target. We assumed that the cognitive load is higher in the active oddball task compared to the neutral condition.

This design allows two comparisons. The first is a comparison between ERPs produced by the same physical stimuli presented under two different conditions. According to García-Larrea et al (1992), such a comparison assesses the changes of vigilance and attention prompted by the subject's involvement in the oddball task. The second comparison is a classical one between ERPs produced by the standard and by the target stimuli of the oddball task. The component known as P300 elicited by the target stimuli is generally larger in comparison with this component elicited by the standard stimuli (Donchin and Coles, 1988; Ruchkin et al, 1980a; Ruchkin et al, 1988; Verleger, 1988). The amplitude of P300 is assumed to be proportional to the degree of updating of the memory representation of the context in which the stimulus is presented (Donchin and Coles, 1988). Late slow wave positivity following P300 is also enhanced with increasing task demands; evidence exists that the two components can be distinguished and opposite changes in amplitude can occur (Ruchkin et al, 1980a; Ruchkin et al, 1988). The late slow wave component is generally interpreted as reflecting a final stage of evaluation of stimuli and additional efforts involved in the categorisation of stimuli. In the present study, we analysed both kinds of positivities by dividing the post-stimulus epoch into two parts. The first window ranged from 250-574 msec post-stimulus onset and included the 'classic' P300, while the late positive slow wave was included in the second window, ranging from 576-900 msec. The effects of a sedative and a non-sedative tranquillizer on both P300 and subsequent late positivity were evaluated in order to determine the effects of these drugs on cognitive functions.

4.1. Material and methods

Twenty four students (6 males and 18 females with an average age of 21 years), participated in the experiment. Subjects reported that they were not currently using medication and were declared healthy by a medical doctor prior to participation. In addition, the study was approved by the medical-ethical committee of the University of Nijmegen and participants signed an informed consent form.

Subjects were randomly allocated to three groups, each consisting of eight subjects. The first group received 10 mg diazepam (Valium®), the second group 10 mg buspirone (Buspar®) while the third group received 10 mg placebo (Coerulea®). All drugs were given orally. The same 10 mg dose was chosen for both psychoactive drugs, since these drugs have an equivalent potency (Boulenger et al, 1989; Seidel et al, 1985). The time between drug intake and the beginning of testing was approximately 45 minutes. During this time, Ag-AgCl EEG electrodes were fixed with collodion at the central (Cz) and parietal (Pz) scalps sites (Jasper, 1958). One electrode was placed above the right eyebrow and another at the right external can thus to record electro-ocular activity. The reference electrode was fixed to the right mastoid, whereas the ground electrode was placed on the right arm. Impedance was less than 3 kOhms in all leads. The high pass filter was set at 0.15 Hz and the low pass filter at 100 Hz. On each trial, the EEG was sampled every 2 msec for 1000 msec, starting 100 msec prior to stimulus onset. The EEG was visually checked off-line for electro-occulographic activity and artifacts. Trials containing eye movements or artifacts were excluded from subsequent analysis. Trials in the oddball task in which no response to the target was given or where a false reaction to a standard was given, were also excluded.

Two series of stimuli were presented, both with an interstimulus interval of 1900 msec. In the first series, 200 identical tones (1500 Hz, 70 dB, 100 msec) were presented. No motor responses were required in this series and subjects were only asked to listen to the stimuli. This was the passive, neutral condition. In the second series, the same tones as used in the first series were used as standard stimuli in an active, oddball condition. Standards were mixed with target stimuli (1750 Hz, 70dB, 100 msec tones). In total 400 stimuli were presented in the oddball condition (80% of standards intermixed with 20% of targets). Subjects were instructed to push a hand-held switch when they detected the target. They were asked to react as quickly as possible, but were also informed that accuracy was prefered above speed. Reaction times, omissions, and false alarms were also measured. Subjects were given practice trials with the standard and target stimuli before the start of the oddball task. While tones were presented, subjects were asked to fix their eyes on a point located 180 cm in front of the subjects and 125 cm above the floor. After the two-tone-series had been administered, subjects completed a

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Subjective Alertness Scale (De Sonneville et al, 1984).

The amount of positivity at Cz and Pz was evaluated in the epoch ranging from 250 through 900 msec after stimulus onset. This epoch was divided into two equal windows; the first ranging from 250 till 574 msec and the second from 576 till 900 msec. Two major comparisons were made. In the first comparison, the positivity elicited by the homogeneous neutral stand and stimuli was subtracted from the positivity elicited by the standard stimuli used in the oddball task. In the second, classical, comparison the positivity elicited by the standard stimuli in the oddball was subtracted from the positivity evoked by the target stimuli. These differences were firstly evaluated by a t-test for dependent samples and analysed with a two factor analysis of variance with drug (3 levels) as the between subjects factor and electrode position (2 levels) as the within subjects factor. Contrasts between diazepam and placebo, buspirone and placebo, and buspirone and diazepam were tested. In order to reduce the large individual differences and to increase the homogeneity of variance, a square root transformation was applied to the data. In addition, the maximum amplitude of P300 evoked by the target was determined, as the most positive peak between 250 and 574 msec. Drug effects on reaction times, number of omissions, false alarms and subjective alertness data were determined by a one factor (three levels) univariate ANOVA.

4.2.   Results
4.2.1.   Comparison of ERPs induced by a standard stimulus in the neutral and oddball condition

ERPs associated with the standard tones in the neutral and oddball conditions are shown in Figure 1. Table 1 give the values of the differences between these conditions and the results of the relevant statistical tests. Based on the data in the figure and table, it can be inferred that there was positivity after placebo and buspirone for both the Cz and Pz electrodes, and for both windows, implying that the standard stimulus in the oddball condition elicited more positivity than the same stimulus presented in the neutral condition.

However, the ERPs of the diazepam did not show more positivity in the oddball condition. When the groups were compared directly, the buspirone group showed more positivity at Pz in the 250-574 msec window than the diazepam group (F=5.88, df=1,21, p<.02).

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Figure 1 A comparison between ERPs elicited by a standard stimulus in the neutral and oddball condition in the placebo (1), buspirone (2) and diazepam (3) groups. ERPs of the neutral standard tones are presented by a thin line, while ERPs of the standard oddball tones are indicated by a thick line. Square root transformed amplitudes of the ERPs are on the Y-axis; positivity is directed upwards and time is in milliseconds.

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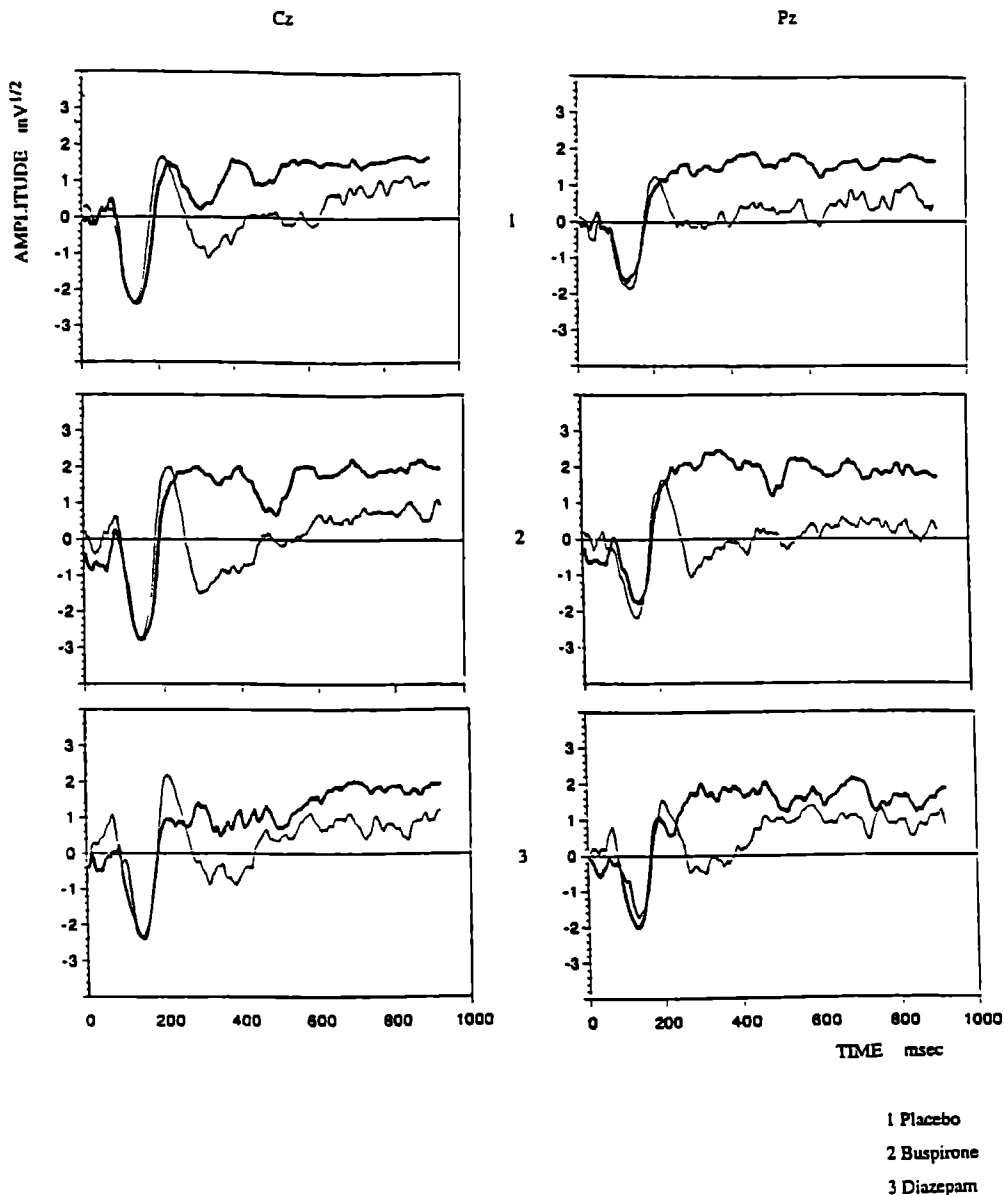
Table 1 Means and SEMs of the difference in positivity with p-values (t-test for dependent samples) between the standard stimuli in the neutral condition and the standard stimuli in the oddball condition for the Cz and Pz electrode position in the placebo, buspirone and diazepam groups.

Electrode	Window 250-574 msec	p-value	Window 576-900 msec	p-value
Cz electrode				
Placebo	12.1 ± 5.5	.06	9.6 ± 3.4	.03
Buspirone	20.6 ± 4.6	.01	16.1 ± 5.4	.02
Diazepam	7.1 ± 7.3	.4	6.4 ± 5.5	.3
Pz electrode				
Placebo	15.1 ± 3.8	.01	12.4 ± 3.8	.01
Buspirone	23.2 ± 2.0**	.01	16.2 ± 4.1*	.01
Diazepam	9.3 ± 5.5	.1	4.4 ± 6.0	.5

* differs marginally significant diazepam; ** differs significantly from diazepam

4.2.2. Comparison of ERPs induced by standard and target stimuli in the oddball condition

ERPs elicited by the target and the standard in the oddball task of the three groups are presented in Figure 2. The corresponding difference values and the results of the statistical tests are shown in Table 2. The difference at Pz between the positivity associated with the two stimuli was significant in the 250-574 msec window for the placebo group and marginally significant for the diazepam group. For the buspirone group this difference was not significant. This implies that the ERP elicited by the target contained more positivity at Pz than the ERP evoked by the standard for the placebo and the diazepam group. At Cz this difference was not significant. The contrasts for the evaluation of the drug effects did not result in significant differences.

Analysis of the maximum value of the positivity in the first window (the P300 peak) indicated that the amplitude of the P300 elicited by the target at Cz was significantly reduced after diazepam in comparison with buspirone (respectively mean and SEM: diazepam 6.2 1.7, buspirone 11.4 1.8; F=4.3, df=1,21, p<0.05). At Pz, this difference was not significant (diazepam 10.3 2.0, buspirone 15.4 2.5).

Figure 2 A comparison between ERPs elicited by a standard and a target stimulus in an oddball condition in the placebo (1), buspirone (2) and diazepam (3) groups. The ERP of the standard stimuli is indicated by a thin line and the ERP of the target by a thick line. Square root transformed amplitudes of the ERPs are on the Y-axis; positivity is directed upwards and time is in milliseconds.

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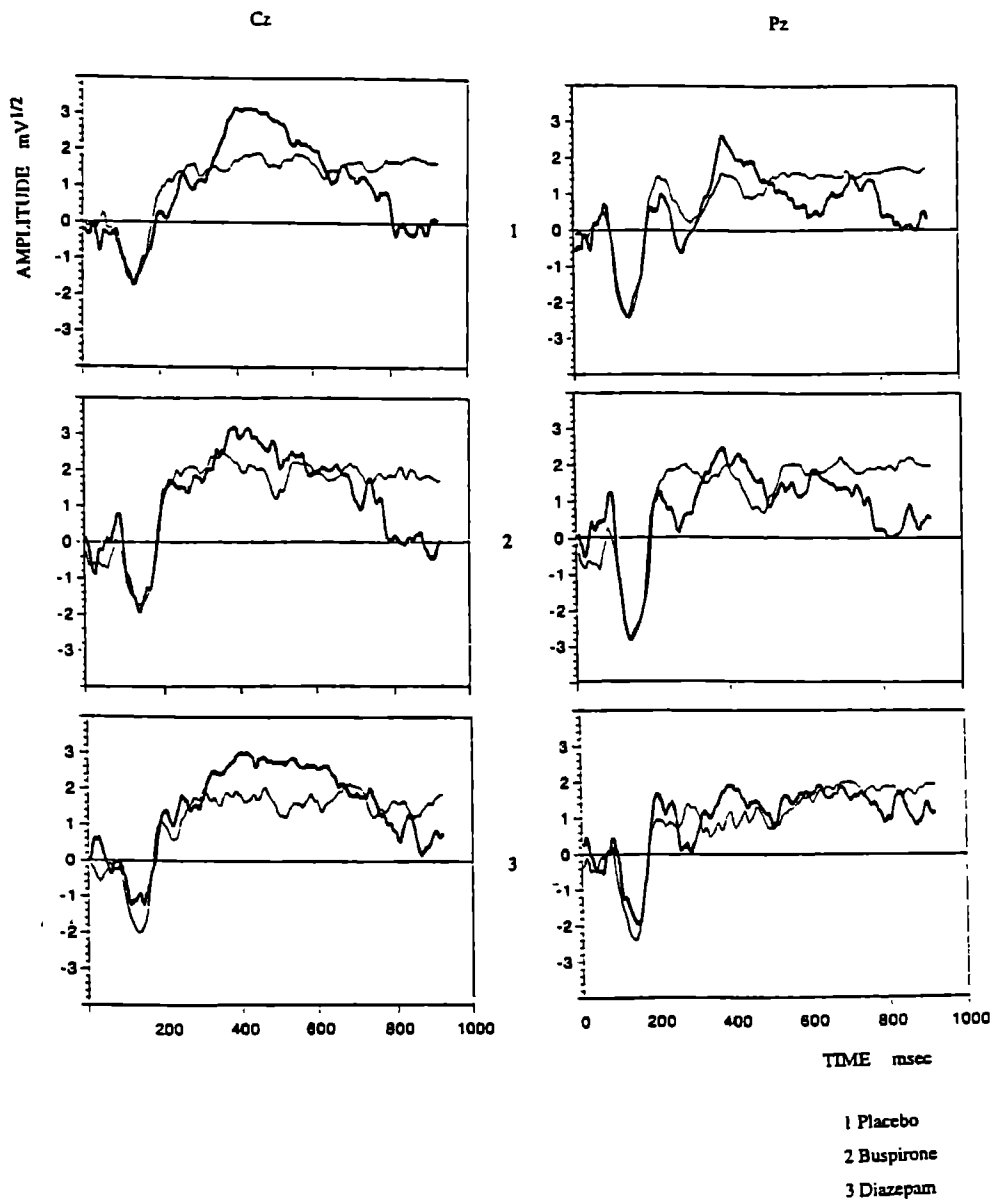
Table 2 Means and SEMs of the difference in positivity with p-values (t-test for dependent samples) between the target and standard stimuli in the oddball task for the Cz and Pz electrode positions in the placebo, buspirone and diazepam groups.

Electrode	Window 250-574 msec	p-value	Window 576-900 msec	p-value
Cz electrode				
Placebo	3.6 ± 4.8	.4	-7.0 ± 3.4	.08
Buspirone	1.9 ± 3.5	.7	-7.3 ± 5.4	.2
Diazepam	3.5 ± 3.3	.3	0.6 ± 2.3	.8
Pz electrode				
Placebo	10.8 ± 3.7	.02	-4.3 ± 4.0	.3
Buspirone	6.7 ± 4.2	.2	-5.4 ± 4.1	.2
Diazepam	9.2 ± 3.4	.06	1.5 ± 2.6	.6

4.2.3. Drug effects on subjective alertness, reaction times, omissions and false alarms

Table 3 Means and SEMs of the reaction times in milliseconds, of the number of omissions and false alarms in the oddball condition and of the data of the Subjective Alertness Scale.

	Placebo	Buspirone	Diazepam
Reaction time	464 ± 26	456 ± 30	539 ± 30*
Omissions	1.0 ± 0.6	2.4 ± 1.1	13.1 ± 5.0**
False alarms	2.4 ± 1.1	1.0 ± 0.6	3.3 ± 5.7
Subjective alertness	15.3 ± 0.6	16.0 ± 0.7	15.0 ± 0.7

* diazepam differs marginally significant from placebo and buspirone;
** diazepam differs significantly from placebo and buspirone

The relevant data are presented in Table 3. In general, subjects reported only small changes in subjective alertness after drug intake. The effects on reaction time were also small and only marginally significant: buspirone versus diazepam F=3.9, df=1,21, p<0.06; diazepam versus placebo F=3.2, df=1,21, p<0.08. However, there was a significant drug effect on omissions: buspirone versus diazepam F=6.7, df=1,21, p<.02; diazepam versus placebo F=8.45, df=1,21, p<0.01. Subjects under the influence of diazepam made more omissions in comparison with placebo and buspirone.

4.4. Discussion

The results of this experiment confirm and extend those obtained by García-Larrea et al (1992). First, we found that ERPs to standard tones in an oddball task were more positive than the ERPs to the same standard tones in the neutral, passive condition. This increase in positivity was evident in both time windows and reflects an effect on both P300 and late slow wave positivity. Following García-Larrea et al (1992) we propose that this reflects the increased vigilance and attention associated with the subjects' involvement in the oddball task. Importantly, the increase in positivity found in the placebo and buspirone groups was not significant in the diazepam group. Furthermore, there was more positivity at Pz in the buspirone group in comparison with the diazepam group. These data suggest that for the diazepam group the level of vigilance and attention does not increase to a level which is sufficient and present in the other two groups. Surprisingly, the different groups did not differ in their subjective evaluation of alertness. It could be that the long-lasting and tiring task reduced subjective alertness in all groups. However, accuracy (the number of omissions) was impaired in the diazepam group.

The comparison between ERPs elicited by targets and standards revealed a clear enhancement of positivity (at the Pz electrode) to the target stimuli in the placebo group in the 250-574 msec window. This enhancement was smaller in the diazepam group, while it was almost absent in the buspirone group. A specific analysis of the P300 component showed a reduction (at Cz) in the diazepam group. Interestingly, no drug effect was found for positivity in the second window. The reduction of the amplitude of P300 elicited by target stimuli after diazepam is in line with the results of Ray et al (1992) and suggests that some aspect of cognitive processing (such as memory updating) is impaired by the drug. However, this interpretation must be qualified by the observation that, while P300 was maximum at Pz (Duncan-Johnson and Donchin, 1982; Pritchard, 1981), the drug effect was significant at Cz. It is possible that this reflects a topographical differences in the regional distribution of benzodiazepine-GABA receptor densities (Scheuler, 1990).

In conclusion, we propose that the reduced differences in positivity between the passive and active conditions and a decreased amplitude of the target P300 after diazepam intake are both related to impairments in information processing. These impairments are also reflected in poorer overt performance and expressed in more omissions and longer reaction times. In contrast, the non-sedative anxiolytic buspirone does not appear to influence ERPs or overt performance in the same way, suggesting that this drug does not impair cognitive processing (Boulenger et al, 1989; De Maio, 1988, Goldberg and Finnerty, 1982). However, it is important to note that there are reports which indicate some adverse, diazepam-like effects of

buspirone, such as increases in motor and total reaction times and a decrease in subjective alertness after acute and chronic administration (Alford et al, 1991). In this regard, the absence of a difference in positivity between ERPs to targets and standard in the oddball task may be significant. This result points to a need for further study of the effects of buspirone on event related potentials.

AUDITORY EVENT RELATED POTENTIALS IN A NEUTRAL AND AN ODDBALL TASKS: EFFECTS OF LEVEL OF DIFFICULTY AND MOTOR RESPONSES ON SLOW WAVE POSITIVITY[4]

Abstract - Late components in auditory event related potentials are particularly sensitive to various types of cognitive processes. In a regular oddball condition two types of slow wave positivity can be distinguished: P300 and late slow wave positivity. The question is investigated whether these two types of positivity can independently be influenced by manipulations of cognitive load. Task variables were varied in two ways. Firstly, the level of difficulty of the oddball task was varied by creating a large difference ('easy condition') and a small difference ('difficult condition') between standard and target stimuli. Secondly, both conditions were tested with and without demanding a motor response on the target stimuli. An identical target tone was used in all oddball tasks. This tone was also presented as a neutral stimulus in a series of tones also with and without the instruction to perform a motor response. Positivity was determined in two time windows, the first ranging from 250 till 525 msec, in which P300 is assumed to occur, and the second ranging from 525 till 800 msec, in which late slow wave positivity can be seen. In general, positivity was most clearly expressed in the first window at the parietal location. Motor responses enhanced especially positivity in this first window. On the other hand, the degree of difficulty was expressed in more positivity in the second window. The level of difficulty was also evident from slower reaction times. It can be concluded that the positivity in the first window, corresponding with P300, becomes visible either by enhanced mental load by the oddball situation or by requiring a motor response, but not by the level of difficulty of the oddball. The difference between the easy and difficult oddball condition is mainly expressed in the amount of late slow wave activity, seen in the 525 till 800 msec window. These findings underline the conclusion that different types of late positivity are directly related to specific kinds of cognitive activity and that different task manipulations can influence various types of positivity in event related potentials.

5. Introduction

Event related potentials (ERPs) have been studied as indicators of brain activities associated with various types of cognitive processes. Especially the slow wave components in

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[4] Unrug A, van Luijtelaar ELJM, Coenen AML.
Auditory event related potentials in a neutral and an oddball tasks: effects of level of difficulty and motor response on slow wave positivity. Submitted to Journal of Psychophysiology 1997.

the ERPs, roughly occurring after 250 msec, are sensitive to psychological variables and information processing (Squires et al, 1975; Courchesne et al, 1977; Johnson, 1986; Verleger, 1988). Traditionally, an oddball paradigm is used to evoke slow wave positivity. In many experiments it was found that an enhancement of these slow ERP components, e.g. P300, runs in parallel with an increase in task demands or in cognitive load (Kügler et al, 1993). The amplitude of P300 might also be related to other psychological constructs such as expectancy, task relevancy, and selective attention (Squires et al, 1975; Kügler et al, 1993). Polich (1989) reported that the passive or active character of the oddball can modulate the amplitude of P300 elicited, with a larger P300 in the active condition in which a motor response to the target is required. Following P300, another type of slow positivity have been described in the oddball ERP: 'late slow wave positivity' (Squires et al, 1975). It has been suggested that an increase of this late positivity can be found when the possibilities of stimulus detection are decreased and the tasks demands are increased (Ruchkin et al, 1980b). It seems further that late slow wave activity occurs without changes in P300, suggesting that P300 and late slow wave activity might be controlled by different mechanisms (Ruchkin et al, 1980a; Ruchkin et al, 1980b; Roth et al, 1978). The two positive waves differ also in another characteristic: late slow wave activity shows a progressive shift in polarity from positivity at parietal to negativity at frontal sites. In contrast, P300 is always positive and its amplitude increases from frontal to parietal (Squires et al, 1977). These different properties of the two positive components underline the possibility that they might be governed by different controlling mechanisms. In a recent study based on a paradigm described by García-Larrea et al (1992), we studied also slow wave positivity (Unrug et al, 1997). Positivity was revealed when the ERP elicited by a neutral stimulus was subtracted from the ERP evoked by the same stimulus as used as the standard in an oddball condition. This positivity mainly occurred parietally and over a long time. Although little is known about this type of positivity, it became clear that it was related to the increased vigilance and attention associated with the subjects' involvement in the oddball task. We hypothesised that if we could succeed in further enhanceing vigilance and attention by an increase of cognitive load, this could give rise to an even stronger increase slow wave positivity. We further speculated that this could be done by an increase in the demands of the task, by a rise in the level of difficulty in the oddball task, or with other changes in task demands. We supposed that these demands are related to slow wave activity. To further explore the relationship with P300, we also included a task manipulation, focused on an exclusive change of the amplitude of P300, i.e. the passive versus active character of the task (Polich, 1987).

Thus, the purpose of the present experiment was to investigate the relationship between various types of positivity. Two parameters were manipulated: the level of difficulty of the oddball task and the requirement to make a motor response or not. To that end, two auditory

oddball conditions were created: one with a small difference between the standard and the target stimulus (considered as the difficult task) and one with a large difference between these stimuli (considered as the easy task). The oddball tasks were presented twice, once without and once with the requirement to make a motor response. Finally, the same stimulus used as target in both oddball conditions was also used as a neutral stimulus in a tone series preceding the oddball series. ERPs obtained from these identical stimuli were compared in order to learn whether this type of positivity was also sensitive for the same manipulations in cognitive load. It is hypothesised that the motor response will influence positivity of P300, and the level of difficulty slow wave positivity over a long time domain or only restricted to the domain following P300.

5.1. Methods and materials

Eight healthy students (3 males and 5 females) with an average age of 21.5 years (range 18 till 25) served as subjects. They agreed to participate in the experiment and signed an informed consent. All subjects were right-handed and had normal hearing capacities. Three Ag-AgCl EEG electrodes were fixed with collodion along the midline at frontal (Fz), central (Cz) and parietal (Pz) scalp sities (Jasper, 1958). The reference electrode was fixed to the right mastoid. Two electrodes were used to record the electro-ocullar activity. They were placed above the right eyebrow and the right external canthus. The ground electrode was placed above the left eyebrow. Prior to the electrode placements, the skin at the electrode sites was cleaned with alcohol. Impedance was less than 3 KOhms in all leads. The high pass filter was set at 0.016 Hz and the low pass filter at 30 Hz.

Participants were subjected to one experimental session in which all data were collected. Before and after a ten-minute-lasting halfway-break, three series of stimuli were presented, thus six in total. During each series, subjects were asked to fix their eyes at a point 100 cm in front and 130 cm above the floor. The session started with the presentation of 200 neutral 1750 Hz, 70 dB, 100 msec tones. Next, the first oddball task was presented. The same tones that were used as neutral stimuli were now used as the target stimuli in a classical oddball paradigm. The target stimuli had a probability of 20% and were, in a Bernoulli sequence, in 80% of cases intermixed with the standard stimuli. The latter were 1500 Hz tones with the same intensity and duration. This second series of tones was followed by a second oddball task, again with the same stimuli as target stimuli, but now intermixed with standard stimuli resembling the target tones more. In this case, the standard tones were tones of 1730 Hz, 70 dB, 100 msec. In total, 400 stimuli were presented in each of the oddball conditions. In these tasks, which were all presented before the break, subjects were instructed to make a motor response (M+) when they

perceived the target stimuli by pressing a hand-held switch. In the neutral task, they were asked to respond to every stimulus presentation. They were asked to react as quickly as possible, but they were also instructed that accuracy was preferred above speed. The presentation of each oddball task was preceded by a few learning trials. The interstimulus interval for each task was randomly varied between 1100 and 1300 msec. The variability of this interval was exactly the same for each task. After the break, all series of stimuli were presented again and in the same order, but now motor responses were not demanded (M-). Subjects were instructed to pay as much attention to the stimuli as they did before.

The EEG was sampled at 5 msec per point. Sampling and storage started 100 msec before stimulus onset in order to establish a prestimulus baseline. After stimulus onset data were sampled and stored for 800 msec. The EEG was checked off-line for artefacts. Epochs with samples exceeding the preamplifier range in all channels including the EOG were rejected. ERPs were corrected for prestimulus differences from zero. Averaged ERPs for each subject consisted of 70-75% of trials. The difference scores between the mean amplitude of the ERPs elicited by the standard and target stimuli were chosen for analysis. This was called comparison 1 and was performed both for the easy and for the difficult oddball tasks. The amount of positivity in the time domain between 250 and 800 msec was divided into two equal parts, from 250 till 525 msec (first window) and from 525 till 800 msec (second window). The time-domain of the first window is assumed to reflect P300, whereas the second window is thought to reflect late slow wave positivity. A second difference score was obtained in comparison 2. The mean amplitude of the ERP from the neutral stimuli was subtracted from the mean amplitude of the ERP from the target stimuli used in both oddball conditions. The presence of positivity (the difference scores) was evaluated with t-tests for dependent samples. Differences between conditions were analysed according to a three factor analysis of variance (ANOVA) with electrode position (3 levels), motor response (2 levels), and level of difficulty (2 levels), all as within groups factors. The effects of the motor response on the ERP elicited by the neutral stimuli was analysed with a t-test for dependent samples. Response latencies were analysed with a one within group factor (three levels neutral stimuli, easy and difficult oddball) ANOVA, followed by post-hoc tests.

5.2. Results
5.2.1. Comparison 1: ERPs evoked by standard and target stimuli

Figure 1 and 2 depict the ERPs obtained in the four oddball conditions. Means and SEMs of the amount of positivity after subtraction the positivity of the ERPs elicited by the standard stimuli from the positivity elicited by the target in the first and second window are

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presented in Table 1. In general, the difference between the two ERPs yielded positivity in the first window. This implies that the ERPs elicited by the target stimuli contain more positivity than the ERPs evoked by the standard stimuli. Significant amounts of positivity occurred in all four variants of the oddball conditions (easy as well as difficult; with and without motor response). This although the majority of the significant conditions were found at Cz and Pz and for the M+ conditions. In one case negativity was found, which reached a significant level. This was at Fz for the easy oddball M- condition.

The three factor ANOVA on the data of the first window indicated more positivity for the M+ than for the M- conditions (F=-13.11, p<0.01, df=1.7), no effect of task difficulty and an electrode position effect (F=55.69, p<0.01, df=2.14). Post-hoc tests showed more positivity at Pz than at Cz and Fz. There were no significant interactions, except one marginal first order interaction between electrode and motor response (F=3.25, p<.07, df=2.14). Post-hoc tests showed more positivity at Pz for the M+ than for the M- condition.

In the second window both positivity and negativity were found: a significant amount of positivity was found at Pz for the difficult oddball M+ condition and a significant amount of negativity was found at Fz and Cz for the easy oddball M- condition (Table 1). The ANOVA on the data of the second window showed a difficulty effect: the difficult oddball induced more positivity than the easy oddball conditions (F=9.46, p<0.02, df=1.7) and an electrode effect (F=23.33, p<0.01, df 2.14). Post-hoc tests showed more positivity at Pz than at Cz and Fz. There were no first or second order interactions.

Table 1 Means in microvolts and standard errors (SEM) of the positivity in the first (250-525 msec) and the second window (525-800 msec) at Fz, Cz and Pz for the four oddball tasks. Positivity was obtained by subtracting the ERP of the standard from the ERP of the target stimulus. Easy and difficult (Diff.) tasks with a motor response are indicated as 'M+', tasks without a motor response as 'M-', p-values are indicated.

	Easy oddball M+ Mean ± SEM p	Easy oddball M- Mean ± SEM p	Diff. oddball M+ Mean ± SEM p	Diff. oddball M- Mean ± SEM p
First window				
Fz	0.48 ± 1.5 .8	-1.70 ± 0.5 .02	0.91 ± 1.1 .5	-0.52 ± 0.7 .5
Cz	3.98 ± 1.4 .03	0.43 ± 1.2 .7	3.32 ± 1.0 .01	0.29 ± 0.8 .7
Pz	7.63 ± 1.7 .01	2.22 ± 0.8 .04	5.64 ± 1.3 .01	2.13 ± 1.0 .09
Second window				
Fz	-0.20 ± 1.3 .9	-4.16 ± 1.1 .01	-2.52 ± 1.2 .08	-1.20 ± 0.9 .2
Cz	0.14 ± 1.3 .9	-3.89 ± 0.9 .01	0.44 ± 1.1 .7	-0.33 ± 0.7 .7
Pz	1.80 ± 0.9 .1	-0.47 ± 1.0 .7	3.00 ± 1.1 .04	1.83 ± 0.9 .1

Figure 1 Grand average of ERPs elicited at Fz, Cz and Pz by target and by standard stimuli in two easy oddball tasks. The easy oddball with motor response (M+). The easy oddball without motor response (M-). The ERP of the target is drawn in a solid line and the ERP of the standard in a dashed line. Amplitudes of the ERPs are on the Y-axis (from -15 till 15 microV); positivity is directed downwards and time is in milliseconds (from -200 till 800 msec).
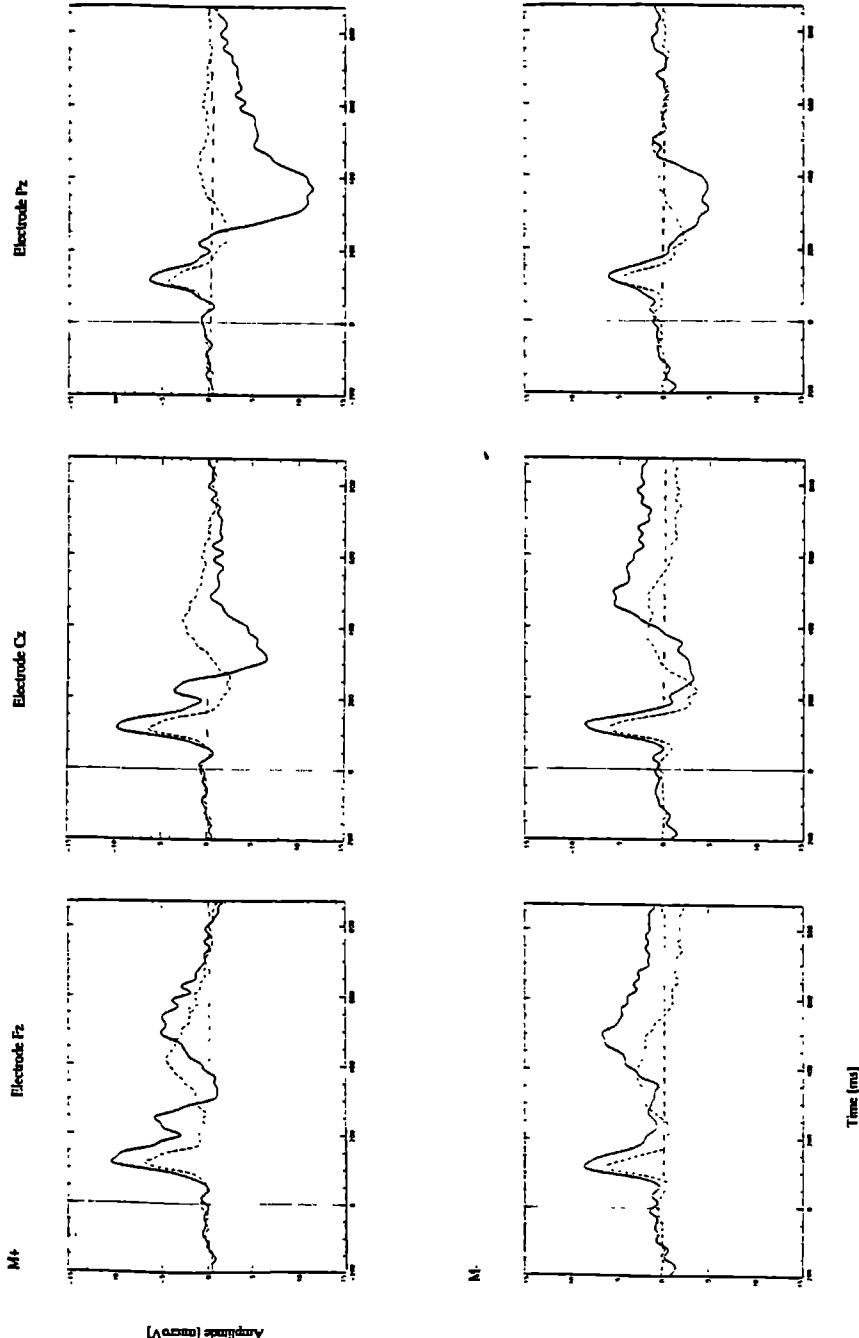
Figure 2 Grand average of ERPs elicited at Fz, Cz and Pz by target and by standard stimuli in two difficult oddball tasks. The difficult oddball with motor response (M+). The difficult oddball without motor response (M-). The ERP of the target is drawn in a solid line and the ERP of the standard in a dashed line. Amplitudes of the ERPs are on the Y-axis (from -15 till 15 microV); positivity is directed downwards and time is in milliseconds (from -200 till 800 msec).
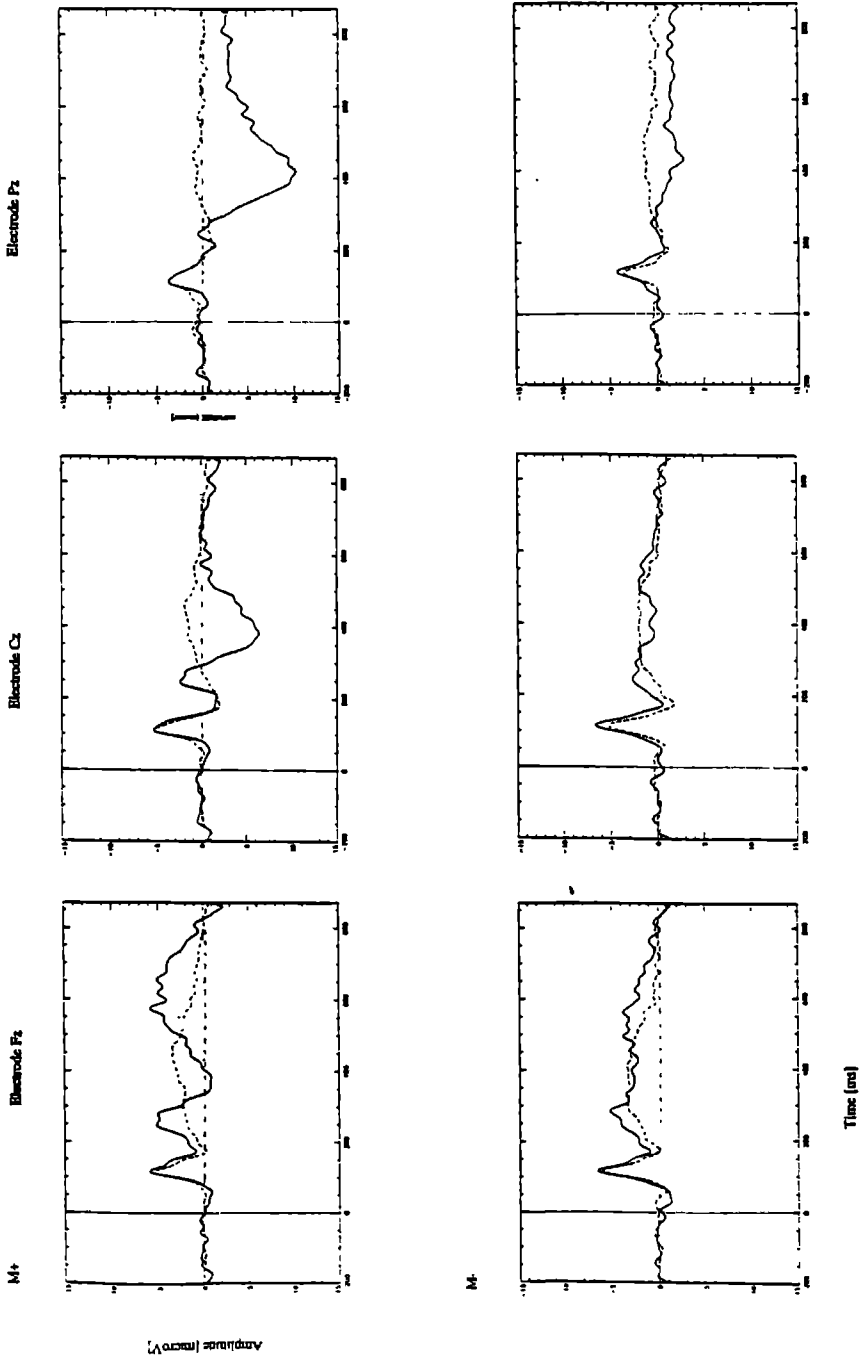
5.2.2. Comparison 2: ERPs evoked by neutral and target stimuli

Means and SEMs of the amount of positivity after subtraction of the ERPs elicited by the neutral stimuli from the ERPs elicited by the target in the oddball task are presented in Table 2. Figure 3 depicts the ERP at Fz, Cz, and Pz of the same stimulus under neutral, easy and difficult oddball conditions, with and without motor responses.

From Table 2 it can be inferred that there in general was a tendency for more negativity in the first and second window at Fz and at Cz, with some significances. A completey different picture emerged at Pz. In general there was positivity which was significant in the first window, for the easy as well as for the difficult oddball M+ tasks.

The ANOVA for the first window revealed a main effect of the electrode position (F=42.75, p<0.01 df=2.14). From the post-hoc test it appeared that the positivity was significantly larger at Pz than at Cz and Fz. A significant interaction between electrode position and motor response was found for positivity in the first window (F=6.40, p<0.01, df= 2.14). Post-hoc tests showed that the motor response largely contributed to positivity at Pz, but not at Fz. There were no other interactions.

Some negativity was found in the second window at Fz and Cz. This reached significancy at Fz for the difficult oddball M+ and at Cz for the easy oddball M- condition. The second window yielded positivity at Pz, which was significant for the difficult M+ oddball. There was an electrode effect (F=25.28, p<0.01, df=2.14) and again positivity at Pz was larger than at Fz. There were no other main effects or interactions.

Table 2 Means in microvolts and standard errors (SEM) of late positivity in the first (250-525 msec) and the second window (525-800 msec). Positivity was obtained by subtracting the ERP of the neutral stimulus from the ERP of the target stimulus for the easy and difficult (Diff.) oddball series, with ('M+') and without a ('M-') motor response, p-values are indicated.

	Easy oddball M+ Mean ± SEM p	Easy oddball M- Mean ± SEM p	Diff. oddball M+ Mean ± SEM p	Diff. oddball M- Mean ± SEM p
First window				
Fz -1.13 ± 1.7 .5	-0.77 ± 0.7 .3	0.82 ± 1.2 .5	-0.63 ± 1.2 .6
Cz 2.46 ± 1.9 .2	0.06 ± 1.1 .9	1.87 ± 1.2 .2	-0.15 ± 1.2 .9
Pz 6.75 ± 2.4 .03	2.20 ± 1.2 .1	4.82 ± 1.4 .01	1.17 ± 1.3 .4
Second window				
Fz -1.58 ± 1.3 .3	-2.08 ± 1.8 .1	-3.97 ± 1.3 .02	-0.97 ± 0.8 .3
Cz -0.59 ± 1.3 .7	-2.67 ± 0.7 .01	-0.50 ± 1.1 .7	-0.19 ± 0.6 .8
Pz 2.07 ± 1.2 .2	-0.22 ± 0.9 .8	3.15 ± 1.3 .05	1.54 ± 1.0 .2

Figure 3 Grand average of an ERP elicited at Fz, Cz and Pz by three identical stimuli under neutral conditions and as target in easy and difficult oddball. The ERPs with a motor response (M+) and without a motor response (M-). The ERP of the target of the 'difficult' oddball is drawn in a solid line, the ERP of the target of the 'easy' oddball in a dashed line and the ERP the of neutral tone in a dashed-dotted-dotted line. Amplitudes of the ERPs are on the Y-axis (from -15 till 15 microV); positivity is directed downwards and time is in milliseconds (from -200 till 800 msec).
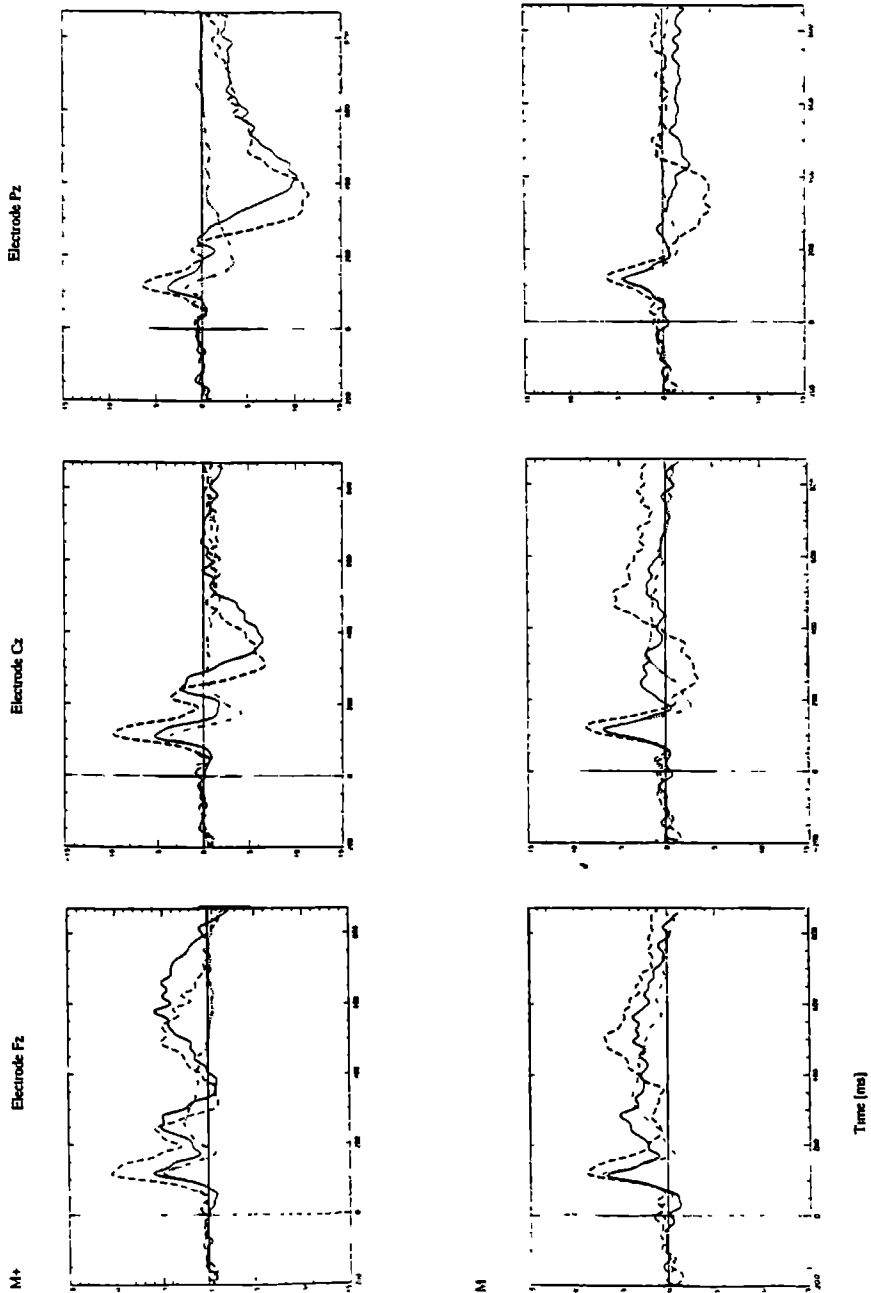
5.2.3. Neutral stimuli with and without motor response

Data and outcomes of the t-tests are presented in Table 3. Neutral stimuli elicited negativity in the early window at Fz and a tendency at Cz. The negativity was no longer significantly present under the M+ condition. A significant effect of motor response (less negativity or more positivity) was found at Fz and Cz for the first and at Fz for the second window. Electrode position was significant for the early window in the M- condition (F=27.07, p<.0001, df 2,14) and for the late window in the M+ condition.

Table 3 Means in microvolts and standard errors (SEM) of the positivity in the first (250-525 msec) and second (525-800 msec) window at different electrode positions, for the neutral stimulus with motor resonse (M+) and without the motor response (M-), p-values are indicated.

	Neutral M+ Mean ± SEM	p	Neutral M - Mean ± SEM	p	Difference Mean ± SEM	p
First window						
Fz	-0.54 ± 0.9	.6	-2.65 ± 0.5	.01	-2.11 ± 0.8	.03
Cz	0.63 ± 0.8	.4	-1.21 ± 0.6	.07	-1.84 ± 0.7	.03
Pz	0.69 ± 0.6	.3	0.08 ± 0.6	.90	-0.61 ± 0.7	.40
Second window						
Fz	0.81 ± 0.6	.2	-0.49 ± 0.6	.4	-1.31 ± 0.4	.02
Cz	0.99 ± 0.5	.08	0.06 ± 0.6	.9	-0.93 ± 0.5	.10
Pz	-0.07 ± 0.4	.9	0.10 ± 0.5	.9	0.16 ± 0.6	.80

5.2.4. Level of difficulty and reaction time

Reactions times for the tasks in which a motor response was required, expressed in means (msec) and SEMs, were as follows: neutral series 244 ± 22; easy oddball series 331 ± 19; difficult oddball series 483 ± 24. Reaction times increased with increased levels of difficulty (F=41.36, p<.0001, df=2.14). Post-hoc tests (t-tests for dependent groups) showed that the reaction time in the difficult oddball was higher (p<.01) than the reaction time on the easy oddball condition, which was, in turn, higher (p<.01) than the reaction time in the neutral condition. None of the subjects made mistakes in the discrimination of the target from the standard stimuli.

5.4. Discussion

In the present experiment it was established that a simple presentation of a neutral stimulus elicits positivity at Pz, but negativity at Fz. The latter was also reported earlier.by Roth et al (1982; 1984). This negativity might reflect preparatory motor responses and might be reminiscent to the CNV, also since the CNV has a frontal origin (Rohrbaugh et al, 1986). The execution of a motor response under neutral task conditions reduces frontal and central negativity or increases positivity in both windows. In all, it seems that frontal negativity is reduced by the execution of a motor response.

The analysis of positivity as determined by comparison 1 (target minus standard) showed in general positivity in both oddball tasks in the first window. This implies, that the ERPs elicited by the target stimuli contain more positivity than the ERPs evoked by standard stimuli. This is in agreement with data from many others with respect to P300, although not all authors have analysed difference scores as we have done (Kügler et al, 1993; Johnson, 1986; Verleger, 1988; Squires et al, 1975). Positivity occurred in all four variants of the oddball conditions at Pz, although only marginally significant in the difficult oddball without a motor response condition. These data suggest that executing a motor response alone is not a prerequisite to elicit parietal positivity although a motor response largely facilitates positivity in this window.

The effect of electrode position on positivity were already described by Courchesne et al (1977) and by Kügler et al (1993). These authors found also that positivity was largest at Pz. The effects of the motor response (more positivity is elicited when a motor response is required) were also described by Roth et al (1978), Pritchard (1989) and Polich (1987). Before a motor response can be executed, the stimuli have to be perceived, to be evaluated, to be discriminated, and to be compared. The consequence is parietal positivity in the early window, which contains P300. Next, a response can be produced, again eliciting parietal positivity in this window (Duncan-Johnson and Donchin, 1982; Johnson, 1986). This is in agreement with the localisation and the time domain effect described by others (Verleger, 1988; Polich, 1987; Ford et al, 1976). In all, it seems that the positivity in the first window depends on two factors: a general P300 factor and the requirement to make a motor response. It is interesting that both effects were most pronounced at parietal regions.

Quite another effect emerged in the second window. Here, it was found that an increase in difficulty in the oddball increased parietal late slow wave positivity. Squires (1975) also found that the largest late slow wave positivity can be found at parietal zones. Interestingly, the motor response had no effect in this window. The level of difficulty, or the discriminability of the target from the standard, seems to elicit positivity in this window. The motor response was

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also slowed down when difficulty increased, as expressed by enhanced reaction times. According to Ruchkin et al (1980a) the increased amount of positivity in the ERP in this window is due to the increased difficulty of the oddball task. Put into other words: it seems that an increased cognitive load induced by enhanced task complexity is associated with more late slow wave positivity. This means that two factors studied in this work, level of difficulty and presence or absence of a motor response, which both are supposed to increase cognitive load or task demands, differentially affect components of an ERP. The modulation of the level of discriminability increases, as assumed late slow wave positivity, but only in the second window, while the requirement to respond overtly influences positivity only in the first window, which includes P300. It is therefore suggested that the first and second window contain parietal positivities of two different types, controlled by two separate processes which can be modulated relatively independently.

The analysis of the amount of positivity elicited by identical physical stimuli presented in the neutral condition and in the oddball conditions (comparison 2) showed, dependent on the electrode position, positivity and negativity. Positivity was largest at Pz and negativity at Fz. There tended to be more positivity in the first than in the second window. It is of interest that the level of difficulty was without any effect in this comparison, whereas the execution of a motor response yielded significantly more positivity in the first window. In a previous study, a comparison was also made between two identical stimuli presented in different conditions, neutral and as part of an oddball task (Unrug et al, 1997). In agreement with this and with the results of García-Larrea et al (1992), again parietal positivity was found. The interpretation of this type of positivity revealed from comparison 2 is difficult. Based on the general presence of positivity, it is however suggested that the presentation of a stimulus under some cognitive load, such as is the case under oddball conditions, is sufficient to induce this positivity in comparison to the presentation of the same stimulus in a neutral condition. Therefore, we suppose that a general activation effect might account for this overall presence of positivity and that a requirement to make a motor response further enhances this effect. It should be stressed that this type of general positivity might be differentiated from the positivity that was successfully manipulated by the level of difficulty. The positivity that was varied by the necessity to perform a motor response was evident in both comparison 1 and 2.

From the above mentioned results it seems that there are at least some types of late positivity. Firstly, there is the positivity in the first window as revealed from the comparison of the standard and target stimulus. This positivity is most pronounced at Pz, and all factors which elicit P300 might be involved in the generation of this positivity. This positivity was also sensitive for the execution of a motor response. A parsimonious explanation is that this type of positivity is induced by the preparation of the motor response. The second type of parietal

positivity is also revealed by the comparison between standard and target stimuli. This second type is called late slow wave positivity (Squires, 1975), and is only expressed in the second window. It was the only variable which was successfully manipulated by the level of difficulty and should therefore be distinguished as independent from the first type of positivity. The parietal positivity in the first window as revealed from the comparison between neutral and target stimuli shows that identical stimuli presented under cognitive load enhance parietal positivity. It can be questioned whether this positivity is identical or is related to the positivity from the comparison between the standard and target stimuli. In both comparisons the target is involved and the similar localisation further suggests that identical processes are underlying the outcomes of both comparisons. In all, we suggest that two types of parietal positivity were measured in this experiment and are sensitive to different types of manipulation and might be distinguished from each other.

CHAPTER 6

COGNITION AND VIGILANCE: DIFFERENTIAL EFFECTS OF DIAZEPAM AND BUSPIRONE ON MEMORY AND PSYCHOMOTOR PERFORMANCE[5]

Abstract - Effects of a single dose of the anxiolytic buspirone (15 mg) on memory and psychomotor performance were studied in healthy volunteers and compared to those of the classic benzodiazepine anxiolytic diazepam (15 mg). The study was performed in a double-blind, placebo-controlled way. Three groups of 12 subjects were exposed to an extended test battery before and after intake of drug or placebo. Next to this, an evaluation session took place 1 week later. Immediately after intake diazepam exerted major effects on memory, impaired psychomotor performance, and decreased alertness. In particular, long term memory had deteriorated, which was interpreted as anterograde amnesia. One week later, more items were recalled from the predrug session compared to the number of items from the postdrug session; this was interpreted as retrograde facilitation. After intake of buspirone, there were no effects on alertness and vigilance, on psychomotor performance and on memory. One week later, a small memory decrement was noticed for verbal material, which was considered as a sign of anterograde amnesia. These results indicate that effects of anxiolytics on memory can be more easily demonstrated 1 week later than immediately after drug intake and, furthermore, that the disruptive effects of diazepam outweigh the small effects of buspirone. Finally, it was established that the effects of diazepam on cognition might be mediated by its effects on alertness and vigilance and that cognitive effects are not related to the anxiolytic properties of the drug.

6. Introduction

Benzodiazepines are the most prescribed anxiolytic and hypnotic drugs. They are effective and relatively safe and are therefore frequently used. Diazepam (Valium®) is a classic member of the large family of the benzodiazepines and is mainly employed as an anxiolytic. Main disadvantages of these drugs are that tolerance develops and that, in particular when used against stress and anxiety, drowsiness and sleepiness is induced (Ghoneim and Mewaldt, 1990; Taylor and Tinklenberg, 1987). Moreover, benzodiazepines not only cause.sedation and drowsiness but also induce an impairment of psychomotor performance. Studies even suggest that therapeutic doses of these psychoactive drugs impair driving skills with consequences for

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traffic safety, an effect which is potentiated by alcohol. Undoubtedly, there is a relation with the decrease of vigilance and alertness (O'Hanlon et al, 1987). Next to these effects, benzodiazepines induce anterograde amnesia: this means that the recall of information obtained under the influence of these drugs is impaired (Coenen et al, 1989; Ghoneim et al, 1984a, Ghoneim and Mewaldt, 1990; Lister, 1985; Mewaldt et al, 1983). Nevertheless, the information obtained before drug intake is intact, therefore it is thought that the retrieval mechanism works properly and that other stages of information processing are affected, such as the transfer from short to long term memory and the consolidation process (Subhan, 1984). On the other hand, an improvement of the recall of information presented immediately before drug intake can be established. This striking phenomenon is called retrograde facilitation (Ghoneim and Mewaldt, 1990; Taylor and Tinklenberg, 1987). The mechanism of this retrograde facilitation remains to be elucidated, although it has been suggested that this is due to a lack of interference with the items learned after drug intake (Hinrichs et al, 1984). As a consequence of the lowered level of vigilance, the processing of these new items is hampered, leading to a decreased retrograde interference (Hinrichs et al, 1984; Taylor and Tinklenberg, 1987).

Buspirone (Buspar®) is one of the relatively new anxiolytics, not belonging to the family of the benzodiazepines (Riblet et al, 1982). It is currently used in anxiety-related disorders (Goldberg and Finnerty, 1982; De Maio, 1988; Schuckit, 1984). It of interest that buspirone lacks hypnotic and sedative properties and does not influence vigilance (Boulenger et al, 1989; Lader, 1982; Mendelson et al, 1990; Rickels, 1980; Seidel et al, 1985). Presumably as a consequence, buspirone does not alter psychomotor performances as driving skills (Boulenger et al, 1989). Preliminary evidence that its effects on memory are smaller than those of diazepam was already obtained by Lucki et al (1987). The fact that buspirone does not induce sedation and sleepiness is important, not only for practical applications but also for theoretical reasons. A comparison of the cognitive effects of buspirone with those of diazepam offers the opportunity to investigate the contribution of sedation, induced by the classic anxiolytics, on cognition.

The purpose of the present study is to compare the effects of diazepam and buspirone on cognition. This will be done with a neuropsychological test battery previously shown to be sensitive for the effects of diazepam and flunitrazepam (Coenen et al, 1989). More specifically, it will be investigated whether buspirone also induces anterograde amnesia and retrograde facilitation. The second purpose it to investigate whether the differences in side effects between buspirone and diazepam, especially with regard to vigilance, can be held responsible for putative differences regarding cognition. Finally, the question can be answered whether the effects of anxiolytic drugs on cognition are related to their anxiolytic action.

6.1. Methods and materials

Thirty six students, with an average age of 22 years, participated in the experiment and were rewarded for this with Dfl 25,-. Participants did not use any medication; they were medically inspected and declared healthy. Participants were all aware that psychoactive drugs were examined, although they were not informed about the intentions of the research. All agreed and signed an informed consent. A statement of no objection was issued by the responsible authorities of the University of Nijmegen.

Subjects were randomly divided into three groups consisting of six men and six women; subjects of the first group received 15 mg diazepam (Valium®), those of the second group 15 mg buspirone (Buspar®) and persons of the third group received placebo. The day before the experiment subjects had to refrain from alcohol. On the morning of the experimental day they were allowed to have only a low-fat breakfast and tea and coffee were not allowed until the testing was over.

The study was carried out in a double blind way. A dose of 15 mg was chosen for both drugs since this dose is often clinically administered. Diazepam and buspirone are considered to have equivalent anxiolytic properties at doses of 15-25 mg/day (Boulenger et al, 1989; Schuckit, 1984; Seidel et al, 1985). The time course of plasma values of diazepam and buspirone is similar; both reach a peak within 60 min after oral administration (Boulenger et al, 1989). Drugs were administered orally.

The experiment consisted of three parts. The first part was the pre-drug test session, which started at 9.00 a.m. and lasted one hour. Next, at 10.00 a.m., the drug or a placebo was administered, followed by a one hour break. At 11.00 a.m. the post-drug session started and lasted till 12.00 noon. One week later, a 15-min-lasting evaluation session was held in which memory for items presented pre- and post-drug intake were evaluated.

The test battery was designed to measure subjective alertness (De Sonneville et al, 1984), long term memory (word fluency -items trees-, complex figure of Rey, 15-word test version A) and short term memory (digit span test), attention and concentration (Bourdon-Vos, trail making, simple reaction time) and motor performance (finger tapping, peg board, simple reaction time task). Except the Bourdon-Vos test (Vos, 1988), information about all these tests can be found in Lezak (Lezak, 1983). The 15-word test is used as a long term memory test, the immediate recall is considered as a long term memory test as well as the 20-min-later delayed recall. The complex figure test had also to be recalled 20 minutes after its presentation. The same test battery, but with parallel versions (complex figure of Taylor, 15-word test version B, word fluency -items furniture-) was offered in the post-drug part of the experiment.

During the evaluation session subjects were asked to recall the words of the 15 words of

both the pre-and post-drug part of the experiment and to draw again, without any cueing, the figure of Rey as well as that of Taylor.

Differences between groups were analysed with an one-factor analysis of variance with consecutive post-hoc tests according to Scheffé ($p<.05$). Within group analyses were done with t-tests for dependent groups between the pre-drug and post-drug part of the experiment. The difference between the scores of the pre- and post-drug part of the experiment was also used to establish differences between groups. This statistic is purer since it takes into account the pre-drug scores.

6.2. Results and discussion

There was no single difference in any of the tests between the three groups prior to drug intake. All significant differences between the buspirone, the diazepam and the placebo group were found in the post-drug part and in the evaluation session. Means and standard deviations of the post-drug part of the experiment and the statistics are presented in Table 1, whereas the results of the evaluation part, one week after drug intake, are presented in Table 2.

The comparison between the effects of diazepam and buspirone, both administered in a dose having roughly equivalent effects on anxiety (Boulenger et al, 1989; Seidel et al, 1985), showed fairly different results. In general, diazepam induced major performance deficits on various neuropsychological tests. Next to altered subjective effects, subjects felt mentally sedated and physically tired, which is commonly found (Boulenger et al, 1989; Roy-Byrne et al, 1987). These effects are in contrast with those of buspirone which does not alter subjective alertness.

Diazepam, compared to placebo and buspirone, significantly decreased motor performance, as measured with the peg board task. In the finger tapping task and in the simple reaction time task the diazepam group was also slower. This was particularly clear after the analysis of the difference between the pre- and post-drug data. The peg board task seems to be the more sensitive test. The effects of benzodiazepines on psychomotor performance confirm earlier work (Boulenger et al, 1989; Hinrichs and Ghoneim, 1987; Rodrigo and Luisardo, 1988; Seidel et al, 1985). In the attention and concentration tests, the diazepam group tended to do worse than the two other groups: on the trail making A and B as well as on parts of the Bourdon-Vos test significant performance deficits were detected. The time necessary to pinpoint the correct items of row number 22 to 33 was significantly prolonged after diazepam, indicating that only the last part of the task, lasting five to six minutes, is sensitive for diazepam and that in the beginning of the test subjects are able to compensate for the negative effects of diazepam. In addition, subjects omitted also more items, suggesting that their accuracy was decreased. It is

Table 1 Mean and standard deviation of the scores from the neuropsychological tests immediately after diazepam (15 mg), buspirone (15 mg) and placebo.

Tests	Diazepam	Buspirone	Placebo	Scheffé (I)	Scheffé (II)
Subjective alertness					
Total score	13.0 ± 3.4	14.4 ± 2.6	15.9 ± 2.4	D<P	D<P
Word fluency	12.8 ± 5.5	12.8 ± 4.0	13.6 ± 4.8	NS	NS
Digit span					
Forward	8.3 ± 2.2	9.1 ± 1.6	9.8 ± 2.2	NS	NS
Backward	7.0 ± 1.6	8.0 ± 2.7	8.7 ± 1.7	NS	D<B
Complex figure					
Delayed recall	10.5 ± 6.6	22.8 ± 5.4	26.7 ± 3.9	D<P, D<B	D<P, D<B
Interferences	3.3 ± 5.0	1.8 ± 2.7	1.1 ± 1.2	NS	NS
15-word test					
1st recall	5.5 ± 1.5	6.7 ± 1.4	7.8 ± 2.5	D<P	D<P
5th recall	9.7 ± 2.3	12.2 ± 2.1	13.6 ± 2.4	D<P, D<B	D<P, D<B
Delayed recall	4.1 ± 4.0	10.0 ± 3.8	12.6 ± 2.6	D<P, D<B	D<P, D<B
Finger tapping					
Preferred hand	56.7 ± 14.7	60.8 ± 8.5	59.9 ± 12.2	NS	NS
Nonpreferred hand	48.9 ± 11.4	50.9 ± 9.2	52.5 ± 9.0	NS	D<P
Peg board					
Preferred hand	9.5 ± 1.9	8.6 ± 1.0	8.1 ± 0.8	NS	D>P, D>B
Nonpreferred hand	10.4 ± 1.3	8.7 ± 1.0	8.9 ± 0.9	D>P, D>B	D>P, D>B
Reaction time, s	289.7 ± 121	219.0 ± 30	221.6 ± 39	NS	D>P
Bourdon-Vos, s					
Mean row time	10.9 ± 2.3	9.6 ± 1.9	9.8 ± 1.4	NS	NS
Row no 22-33	10.8 ± 2.2	9.2 ± 2.3	9.7 ± 1.5	NS	D>B
Omissions	3.7 ± 3.3	1.2 ± 1.7	0.9 ± 1.7	D>P, D>B	NS
Trail making					
Trail A	29.2 ± 7.1	23.8 ± 5.7	20.4 ± 4.9	D>P	NS
Trail B	26.8 ± 5.9	23.2 ± 5.9	20.9 ± 5.9	D>P	NS
Trail C	34.3 ± 7.0	30.6 ± 10.0	28.0 ± 8.0	NS	NS

In the fourth column the outcomes of the post-hoc tests are indicated (Scheffé I). In the fifth column the outcomes of the post-hoc tests are given after correction for differences between the three groups prior to drug intake (Scheffé II): NS means not significant; D = diazepam, B = buspirone, P = placebo.

striking that only a significant effect was detected for trail A and B, not for C, although the effects went into the same direction. It is also striking, that the variances for trail A are relatively small compared to the variances of B and C. This indicates that trail A is equally simple for all

subjects. Moreover, it shows that simple tasks could be sensitive for effects of diazepam, which is in contrast to what is sometimes stated (Fang et al, 1987).

Diazepam significantly decreased the delayed recall of the complex figure test after drug intake. This indicates the presence of anterograde amnesia for visual material. The results obtained with another long term memory test, the delayed recall of the 15-word test, showed also a decrease after drug intake. If the pre-drug scores were taken as the 100% level, the diazepam group recalled only 33% of the items, the buspirone group repeated 79% and the placebo group 96% of the words. Significant differences between the groups were detected, indicating that anterograde amnesia was present for verbally presented items as well. There were no significant drug effects in the word fluency test; it seemed that subjects after taking relatively high doses of anxiolytics, were perfectly able to retrieve information from their long term memory. This clearly indicates that the process of memory retrieval is not affected by these anxiolytics.

Table 2 Mean and standard deviation of the scores from the neuropsychological tests for the three groups of the evaluation session, one week after drug: diazepam (15 mg), buspirone (15 mg) or placebo intake.

Tests	Diazepam	Buspirone	Placebo	Scheffé (I)	Scheffé (II)
Complex figure					
Pre-drug	20.5 ± 7.6	17.4 ± 6.7	13.8 ± 6.3	NS	D>P, D>B
Post-drug	7.5 ± 4.3	15.5 ± 6.6	11.5 ± 5.7	D<B	D<P, D<B
15-word test					
Pre-drug					
Recall	6.6 ± 3.8	5.0 ± 2.3	5.6 ± 1.7	NS	D>P, D>B
No interferences	0.0 ± 0.0	3.6 ± 3.1	1.5 ± 1.4	B>D	NS
Recognition	11.1 ± 2.6	8.9 ± 3.6	9.8 ± 1.9	NS	NS
Post-drug					
Recall	0.8 ± 1.2	3.7 ± 2.5	5.8 ± 1.0	D<P, D<B, B<P	NS
No interferences	1.5 ± 3.7	2.4 ± 3.2	0.6 ± 0.5	NS	NS
Recognition	7.3 ± 3.1	8.9 ± 4.4	12.0 ± 1.6	D<P	D<P

In the fourth column the outcomes of the first post-hoc test is indicated (Scheffé I). In the fifth column the outcomes of the post-hoc test are given for the difference scores (either with the predrug scores or with the postdrug scores) (Scheffé II). D = diazepam, B = buspirone, P = Placebo; NS = not significant.

One week later, in the evaluation, there were even more drug effects on memory. A distinction should be made with respect to recall of the items presented before and after drug intake. After drug intake, fewer items from the long term memory test were remembered by the buspirone and the diazepam group. This means that anterograde amnesia is demonstrated, but

now for both drugs. An obvious difference between the two drugs is that the amnestic effects of diazepam were already present immediately after drug intake, while the amnestic effects of buspirone took more time to emerge, and were smaller. This might be due to insufficient transfer of information from short to long term memory or to a less efficient storage and consolidation.

The recall of the items presented before drug intake was the opposite: the diazepam group tended to remember more items from the complex figure than the placebo group did, indicating retrograde facilitation for visual material. Retrograde facilitation for the verbal material was not found. Considering the presence of retrograde facilitation for the complex figure, it can be assumed that differences in the modality of the items to be recalled may explain this discrepancy. Another difference between the two long term memory tests is that the number of items to be remembered is considerably higher in the complex figure than in the 15-word test.

A possible explanation of retrograde facilitation is that due to the poor acquisition after diazepam, less interference occurs with the material learned immediately after drug intake. In this sense it is not surprising that subjects of the buspirone group made more interferences: they mixed words from the lists of 15 words from the pre- and post-drug part: in this group there were no indications of retrograde facilitation.

Short term memory, as measured with the digit span test, was also affected after diazepam and not after buspirone. This is again interpreted as anterograde amnesia for diazepam. The digit span forward test did not show significant effects. However, a tendency in the same direction was observed. The digit span backward test was generally performed less well than the forward part, suggesting that the differences in difficulty contribute to the sensitivity of the tests for diazepam. The small effects of diazepam on short term memory contribute to the effects reported on long term memory: a precondition for subsequent recall is a proper transfer from short to long term memory (Lister, 1985; Subhan, 1984).

A final issue is that besides differences between effects of the two anxiolytics on memory, also psychomotor, attention and concentration and subjective feelings, among which sedative effects, were different. In all cases, no effects were found after buspirone, while often clear effects were found after diazepam. This suggests that the cognitive deterioration of diazepam can be due to the side effects of the benzodiazepines. The most likely candidate is of course sedation: the reduced vigilance after diazepam might contribute to a more superficial storage. It also seems clear from the comparison between the two anxiolytics between buspirone and diazepam that the anxiolytic property is not necessary coupled to the cognitive deterioration.

It can be concluded that diazepam causes strong effects on psychomotor and long term memory: anterograde amnesia and indications for retrograde facilitation were obtained while the

retrieval mechanism seems unaffected. Diazepam also slightly educed short term memory; this was considered to contribute to long term memory impairment. In contrast, buspirone did not impair the performance of any of the attention and concentration tests, psychomotor tests and short and long term memory tests; only in the evaluation, one week later, the recall of the 15 words was less and the number of interferences was higher. This latter result underlines the sensitivity of the evaluation procedure, one week after drug intake, in testing psychoactive compounds.

CHAPTER 7

EFFECTS OF THE TRANQUILLIZER DIAZEPAM AND THE STIMULANT METHYLPHENIDATE ON VIGILANCE AND MEMORY[6]

Abstract - Effects on alertness and memory of a single dose of diazepam (10 mg) and the central stimulant methylphenidate (20 mg) were studied in healthy volunteers. It was questioned whether opposite effects of diazepam and methylphenidate are not only observed with respect to alertness but also with respect to memory. It was also questioned whether the two drugs equally affect the first (primacy) and last (recency) items in both the immediate and delayed recall of newly learned words. The experiment was performed in a double-blind, placebo controlled way. 12 Subjects were exposed to a subjective alertness scale and a verbal memory test: a 15-word test. Subjective alertness was found to be decreased after diazepam and increased after methylphenidate. Anterograde amnesia was found after diazepam in the memory test. More specifically, the primacy but not the recency effect was reduced during the immediate recall and both were reduced in the delayed recall. Methylphenidate had no effect on memory, however a ceiling effect might have obscured a putative drug effect. The results of a second experiment excluded this possibility. In all, the data demonstrate opposite effects of the two drugs on subjective alertness, suggesting opposite effects on vigilance. Opposite effects on memory were not established. This demonstrates that changes in alertness do not run in parallel with changes in memory. A scatter diagram, however, suggest a small effect of alertness on immediate recall. The effects of diazepam were also discussed in terms of Atkinson and Shiffrin's memory theory and it seems that diminished rehearsal processes are one of the key factors in explaining diazepam induced amnesia.

7. Introduction

Benzodiazepines are important as anxiolytic and hypnotic drugs. These drugs are considered as effective and relatively safe and that is why they are frequently prescribed. Benzodiazepines also produce adverse effects, such as a reduced level of alertness and vigilance. This has been abundantly demonstrated with objective measurements such as classical vigilance tasks and subjective alertness scales (Koelega, 1989; King, 1992; Unrug et al, 1992). Apart from these effects, benzodiazepines also influence memory processes. Anterograde amnesia is frequently reported to occur as a result of the usage of these drugs (Fang et al, 1987; Ghoneim and Mewaldt, 1990; Unrug et al, 1992). Anterograde amnesia implies that recall of information learned after drug intake is impaired. Although the reason for

this is not well understood, it is thought that an impairment of the transfer of information from short to long term memory and an impairment in storage and consolidation is the cause of this type of amnesia (Hinrichs et al, 1984; Fang et al, 1987; Ghoneim and Mewaldt, 1990; Taylor and Tinklenberg, 1987; Unrug et al, 1992). It is often suggested that the sedative effects, the decreased vigilance or the reduced attention are the underlying factors of benzodiazepine induced amnesia. This leads to a shallower processing of information and so to a less adequate storage of information (e.g. King, 1992 for review). Diazepam (Valium®) is a classic and main representative of this class of drugs known for its amnestic effects (King, 1992).

Methylphenidate (Ritalin®) is a representative of a group of centrally stimulating drugs. Methylphenidate is prescribed against narcolepsy and against attention disorders in hyperactive (attention deficit hyperactivity disorders) children. The paradoxical calming effect of methylphenidate in these children is thought to be related to an increase in cortical arousal, giving rise to an attending to a task (Aman et al, 1984; Shaywitz and Shaywitz, 1991). This effect of methylphenidate may occur in normal children, as well as in young adults (Rapoport et al, 1980; Klorman et al, 1984). Furthermore, an increase in vigilance has been found in healthy young volunteers (Aman et al, 1984, Strauss et al, 1984).

The effects of diazepam and methylphenidate on memory will be described in terms of the Atkinson and Shiffrin (1971) memory model. Three memory components are distinguished in this model: sensory memory (SM), short term memory (STM) and long term memory (LTM). SM is the memory component that receives stimulation from the external environment while STM receives information from both SM and LTM. STM is considered as a memory register which holds current and recently obtained information. LTM is a memory component where information is stored on a relatively permanent basis and which has a large capacity. The capacity of STM is limited and retrieval from STM might only be possible in a limited amount of time (15-30 sec). Rehearsing and coding are considered as control processes in STM. These processes affect transfer of information to and from LTM and govern learning and retrieval. The most important control process is rehearsal: overt and covert repetition of information. Rehearsal has two functions. First, rehearsal maintains information in STM, prevents it from being lost or displaced by other bits of information. A subject can keep information in his or her STM beyond the limited time by rehearsing, but the number of items is strictly limited to about seven. Secondly, rehearsal transfers information from STM to LTM. The second control process, coding, is the adding of appropriately chosen information from LTM to an item which is to-beremembered, providing it with a label, and then rehearsing the entire complex in STM. Consolidation is a storage process of the learned information in LTM (Ashcraft, 1989; Atkinson and Shiffrin, 1971).

The purpose of this study is twofold. First it is questioned whether opposite effects of

diazepam and methylphenidate can be observed both with respect to alertness and memory. The second purpose is to describe in terms of the model of Atkinson and Shiffrin the effects on memory induced by the two drugs. More specifically, it is examined whether both drugs similarly affect the immediate and delayed recall in a free recall verbal memory test and whether primacy and recency effects are equally sensitive for the drugs.

7.1. Methods
7.1.1. Subjects

Six female and six male students with an average age of 24 years (range 19-27), participated in the experiment. Participants did not use any medication in some cases oral contraceptives. They were medically inspected and found to be healthy. The participants were aware that psychoactive drugs were examined and were informed in general terms about the nature of the experiment. All gave their informed consent. The experiment was approved by the medical-ethical committee of the Medical Faculty of the University of Nijmegen (CEOM) and carried out according to GCP norms.

The experiment was performed according to the rules of a three way cross-over design (Latin square). Subjects received an oral dose of 10 mg of diazepam (Valium®), or 20 mg methylphenidate (Ritalin®) or placebo in a double-blind way. The doses were chosen since they are considered to be safe and are often used in psychopharmacological experiments (Camp-Bruno and Hertig, 1994; Hinrichs and Ghoneim, 1987; Miller et al, 1988; Naylor et al, 1985; Roy-Byrne et al, 1987). The day before the experiment the subjects had to refrain from alcohol. On the morning of the day of the experiment the subjects had a low-fat breakfast; tea and coffee were not allowed until testing was finished. There was always a 10-day interval between the test days.

7.1.2. Neuropsychological tests

Considering the fact that opposite effects of diazepam and methylphenidate on vigilance were established earlier with classical vigilance tests (Koelega, 1989; Strauss et al, 1984), an indication of drug induced changes in vigilance will be obtained with Thayer's subjective alertness scale (Thayer, 1986). The 15-word test is a verbal free memory test, earlier found to be sensitive for the effects of diazepam (Unrug et al, 1992). In this test, the words were presented 5 times, each presentation was followed by an immediate free recall. A free delayed recall occurred 20 minutes after the learning session.

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7.1.3. Procedure

Pharmacokinetic studies indicate that following an oral administration of methylphenidate, the plasma concentration rises sharply in the initial 60 minutes (Gualtieri et al, 1982). After this point, blood levels still gradually rise till about 2 h after drug intake but a relative constant plasma level is present 75-150 minutes after intake (Strauss et al, 1984). Tests were given 1 h after drug or placebo intake. Three parallel versions of the 15-word test were used. The versions of the test were counterbalanced within and between subjects. Thayer's scale measured subjective alertness or more specifically, the level of general high activation, the level of general deactivation, and the level of deactivation associated with sleep. The scale was presented 2 h after drug intake. Filler tasks were given between the fifth immediate and delayed recall of the 15-word test and the Thayer scale.

7.1.4. Statistic analysis

The results of the subjective alertness and memory test were analysed with a repeated measures analyses of variance with drug (3 levels) as a within- and order (3 levels) as a between-subject factor since a Latin square design was used. Since there were neither significant order nor order x drug interactions, order was excluded from the analyses. A priori contrasts between methylphenidate and diazepam, between methylphenidate and placebo, and between diazepam and placebo were used to describe differences between drug conditions. Next, correlations between two subscales of the Thayer, general activation and deactivation associated with sleep, and the performance on the 15-word test for each drug group separately were calculated (which, of course, has merely a descriptive value due to the low number of cases per group: n=12).

7.2. Results
7.2.1. Subjective alertness scale

The results obtained from the subjective alertness scales are presented in Table 1. Table 1 and the statistics showed characteristic opposite features of the two drugs. First, diazepam decreased the level of 'general activation' in comparison with methylphenidate and placebo ($F=16.45$, $p<0.01$; $F=6.85$, $p<0.05$, respectively; df were 1,22). Second, the stimulatory effect of methylphenidate (a decreased level of 'deactivation' and 'deactivation associated with sleep') was significant, not only in comparison with diazepam but also with placebo ($F=4.94$, $p<0.05$ and $F=26.74$, $p<0.01$ for methylphenidate vs. diazepam and $F=4.44$, $p<0.05$ and

F=10.04, p<0.01 for methylphenidate vs. placebo; all df were 1, 22).

Table 1 Mean and standard error of the scores from the subjective alertness test (Thayer) after diazepam (10 mg), methylphenidate (20 mg) and placebo.

	Diazepam	Methyl-phenidate	Placebo	DvsM	DvsP	MvsP
General activation	9.8 ± 1.1	13.8 ± 0.7	12.3 ± 0.9	D<M	D<P	NS
General deactivation	16.7 ± 0.6	15.1 ± 1.0	16.6 ± 0.5	D>M	NS	M<P
Deactivation/sleep	15.2 ± 1.2	10.0 ± 1.0	13.2 ± 0.8	D>M	NS	M<P

D = Diazepam, P = Placebo, M = Methylphenidate, NS = not significant

7.2.2. Memory tests

The results of the 15-word test are presented in Table 2. As shown, significant differences in the recall occurred after drug intake. A significant impairment was found after diazepam intake for the fifth immediate recall compared to methylphenidate and placebo (F=9.32, p<0.01; F=4.33, p<0.05, respectively; df were 1,22). Furthermore, the delayed recall indicated an impairment after diazepam in comparison with methylphenidate (F=15.86, p<0.01; df=1,22) and placebo (F=11.83, p<0.01, df=1.22).

Table 2 Mean and standard error of the scores from the 15-word test after diazepam (10 mg), methylphenidate (20 mg) and placebo.

	Diazepam	Methyl-phenidate	Placebo	DvsM	DvsP	MvsP
Immed. recall 1st	6.8 ± 0.9	8.7 ± 0.7	8.8 ± 0.8	NS	NS	NS
Immed. recall 5th	13.1 ± 0.7	14.9 ± 0.1	14.3 ± 0.3	D<M	D<P	NS
Delayed recall	8.8 ± 1.5	14.3 ± 0.3	13.5 ± 0.5	D<M	D<P	NS
5th immed.-Delayed recall	5.3 ± 0.4	0.6 ± 0.1	0.8 ± 0.1	D>M	D>P	NS

D = Diazepam, P = Placebo, M = Methylphenidate, NS = not significant, immed. = immediate.

In order to further characterise the memory deficits found after diazepam administration, the first and fifth immediate and the delayed recall of the 15 words were analysed with respect to primacy and recency effects. The data are presented in Table 3. The first immediate recall of the first 3 words (primacy effect) was already impaired after diazepam in comparison with methylphenidate (F=5.20, p<.05, df=1,22). The delayed recall of the first 3 words was also

impaired after diazepam in comparison with methylphenidate and placebo, respectively (F=13.20, p<0.01; F=13.20, p<0.01, df were 1,22). The immediate recall of the last 3 words (recency) was not differentially affected by the drugs, only the delayed recall. A significant impairment was found for the diazepam group in comparison with methylphenidate and placebo respectively (F=16.27, p<0.001; F=11.04, p<0.001, df were 1,22). The amount of forgetting as measured in the delayed recall after diazepam, tended to be greater for the first 3 words than for the last 3 words (1.58 ± 0.3 vs 1.08 ± 0.4) (means and standard errors of the means). However, only a marginal significant difference emerged (p<0.07).

Table 3 Mean and standard error of the recall of the words from the beginning and the end of the list of 15-word test after diazepam (10 mg), methylphenidate (20 mg) and placebo.

	Diazepam	Methyl-phenidate	Placebo	DvsM	DvsP	MvsP
Word 1-3						
Immed. recall 1st	1.4 ± 0.3	2.2 ± 0.2	2.0 ± 0.3	D<M	NS	NS
Immed. recall 5th	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	NS	NS	NS
Delayed recall	1.9 ± 0.4	2.9 ± 0.1	2.9 ± 0.1	D<M	D<P	NS
5th immed. - Delayed recall	1.1 ± 0.4	0.1 ± 0.1	0.1 ± 0.1	D>M	D>P	NS
Word 13-15						
Immed. recall 1st	2.1 ± 0.3	2.7 ± 0.2	2.6 ± 0.2	NS	NS	NS
Immed. recall 5th	2.8 ± 0.2	3.0 ± 0.2	2.8 ± 0.1	NS	NS	NS
Delayed recall	1.3 ± 0.3	2.7 ± 0.2	2.4 ± 0.2	D<M	D<P	NS
5th immed.- Delayed recall	1.6 ± 0.3	0.3 ± 0.2	0.3 ± 0.2	D>M	D>P	NS

D = Diazepam, P = Placebo, M = Methylphenidate, NS = not significant, immed. = immediate

7.2.3. Correlation between alertness and memory

The sub-scales which showed a significant drug effect, general activation, and deactivation associated with sleep were correlated separately with the recall scores of the 15-word test for each drug. The correlation between 'deactivation associated with sleep' and the first immediate recall in the 15-word test was significant (-.76 p<0.05) after methylphenidate. In the placebo and the diazepam group the correlation's were respectively -.39 and -.36, but they failed to reach significance. The scatter diagram (Figure 1), however, suggests a weak overall relation between both measures of alertness and the performance on the first immediate recall of the 15-word test. The correlations with the fifth immediate and delayed recall were lower than 0.3.

Figure 1 Correlation between alertness measured with two subjective alertness subscales (Thayer) and the performance in the first immediate recall of the 15-word test, D=diazepam, M=methylphenidate, P=placebo.
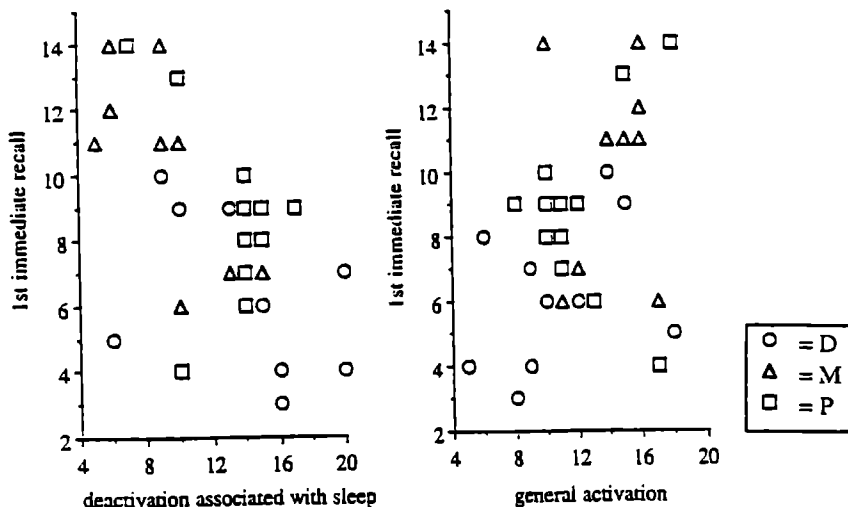
7.4. Discussion

The comparison of subjectively estimated alertness after diazepam and methylphenidate intake showed clear opposite effects. After diazepam subjects felt not only less active but also generally deactivated or even deactivated with a tendency towards sleepiness. Similar changes in alertness and vigilance have been found by Roy-Byrne et al (1987), Boulenger et al (1989), Unrug et al (1992) and Gorissen et al (1995). Methylphenidate increased the subjective feelings of alertness. This is in agreement with others who reported an increase in alertness and wakefulness (Hink et al, 1978; Strauss et al, 1984; Bergman et al, 1991).

Apart from altered subjective effects, diazepam influenced verbal memory, as measured with the 15-word test. Diazepam significantly decreased not only the immediate but also the delayed recall of the 15-word test. This impairment of both the immediate and the delayed recall indicates anterograde amnesia, which is commonly found after administration of benzodiazepines (Mewaldt et al, 1983; Ghoneim et al, 1984; Coenen et al, 1989; Ghoneim and Mewaldt, 1990).

According to the Atkinson and Shiffrin model, the performance on the immediate recall of the 15-word test is dependent on the quality of acquisition of items from SM to STM, on the rehearsal of the items in the STM, and on the transfer of these items to LTM. Since STM is generally intact with this dose of diazepam (Curran, 1986; Ghoneim and Mewaldt, 1990; Lister, 1985; Unrug et al, 1992), it seems that SM including the transfer from SM to STM is not changed by the drug. Furthermore, the model suggests that a less efficient rehearsal process providing transfer of learned information to LTM is causing the performance deficit in the immediate recall of the 15-word test. This explanation is slightly more specific than what was suggested by Curran (1986), Ghoneim and Mewaldt (1990) and Lister (1985). These authors conclude only that the transfer of STM to LTM was impaired. The poor performance in the delayed recall, besides the impaired rehearsal already visible in the immediate recall, might be due to less appropriate rehearsal including coding or impaired consolidation of words into LTM since retrieval processes are commonly not affected by diazepam (Curran, 1986; Ghoneim and Mewaldt, 1990; Lister, 1985).

A more detailed analysis of the first and last 3 words of the 15-word test shows an impaired recall of the words from the beginning of the list for the first immediate recall after diazepam. Subjects under the influence of diazepam forget these words faster than after placebo intake or under the influence of methylphenidate. During the presentation of the first 7 words, the words are put into a rehearsing buffer, and after the presentation of the next items, some of the words presented first are transferred to LTM. These diminished immediate recall scores of specifically the first 3 words indicate the vulnerability of the rehearsals, coding, and transfer processes when diazepam is involved. The impaired recall of the words from the beginning of the list disappeared at the fifth immediate recall trial. This suggests that subjects take advantage of the repeated presentation of the 15 words, probably by rehearsals, but there is also a clear ceiling effect which might obscure putative drug effects.

The recall of the last words of the list of 15 words was not impaired during any of the immediate recalls. These words are still in the STM and therefore no impairment is found for these items. The recall of these words was virtually identical to that of nondrugged subjects. In contrast, the delayed recall of these words was again impaired after diazepam. And again this might indicate the fragility of the LTM memory trace. In all, the data show a higher sensitivity of the first 3 words compared to the last 3 words to being forgotten under the influence of diazepam.

Although correlation in our small samples must be interpreted with caution, there seemed to be a significant correlation between performance of the 15-word test and level of deactivation associated with sleep after methylphenidate, but there was no effect of this drug on memory. Many studies with methylphenidate were devoted to vigilance and attention and only a

few memory studies were undertaken. From the few studies available can be concluded that STM is not affected by this drug, neither were there effects on LTM as determined with a visual version of the paired word test (Aman et al, 1984; Strauss et al, 1984). However, it has to be admitted that the recall scores of the 15-word test were extremely high. A ceiling effect might have prevented the putative increase after methylphenidate. This ceiling effect might be facilitated by the design of the experiment. The same subjects returned 3 times in order to be tested under placebo, diazepam amd methylphenidate and for them the delayed recall of their second or third session was no longer a surprise. This is generally the case if experimentally naive subjects are confronted with the 15-word test during the experiment. This ceiling effect in the recall of the 15-word test was successfully prevented in a second experiment. The 12 subjects (7 men and 5 women) with an age of 18 till 25 years (mean 22.6) were divided into two groups. One group received 20 mg methylphenidate and the second placebo under the same conditions as described above. The number of words to-be-remembered was now 20 and words were presented only twice. Methylphenidate or placebo were administered and after 60 min. the 20-word test was presented. The delayed recall was determined another 30 min. later, and filler tests were given between the immediate recall and delayed recall. Subjective alertness was again measured with the Thayer's scale 60 min later. The level of 'deactivation associated with sleep' was smaller after methylphenidate (8.5 ± 1.9) in comparison with placebo (10.3 ± 0.96), (F=4.47, p<0.05, df=1,22). The results of the 20-word test for methylphenidate were immediate recall (13.3 ± 0.9) and delayed recall (8.1 ± 1.0) and for placebo: immediate recall (14.2 ± 0.9) and delayed recall (8.5 ± 1.2). These data clearly show that there was no ceiling effect. However, a statistical evaluation again did not show differences in either the immediate or the delayed recall of words learned under the influence of methylphenidate and placebo.

A word of caution with respect to the lack of memory improvements in both experiments seems to be justified here. The plasma concentration after methylphenidate rises sharply in the initial 60 minutes but after this point blood levels still gradually rise till about 2 h after drug intake (Gualtieri et al, 1982; Strauss et al, 1984). Therefore the possibility cannot be excluded that only subjective effects were found; these were determined two hours after drug intake while memory tests were scheduled 1 h after intake. However, drug effects of methylphenidate occur earlier than 2 h post drug, as demonstrated for the benchmark of stimulating effects, the heart rate (Strauss et al, 1984). These authors also suggest that there are relative constant plasma concentrations 75-150 minutes postingestion. In all, the results obtained after methylphenidate are not in line with our hypotheses that an increase in alertness induced by a central stimulant might increase the recall of verbal material, expressed in anterograde facilitation.

The results from this experimental work demonstrate that opposite effects of diazepam

and methylphenidate can be found with respect to alertness, but not for memory. This weakens the relationship between alertness and memory processes. Also a decrease in alertness as a result of sleep deprivation does not give rise to memory impairments (Gorissen et al, 1997; Coenen and van Luijtelaar, 1997). On the other hand, a significant correlation between alertness and memory for methylphenidate, explaining about half of the interindividual variance, and a weak, but not extremely low relationship between alertness and the amount of recall which is present in the scatter diagram for all drug groups, suggests some role for alertness in the recall. Factors other than an impairment of alertness or vigilance must also play a role in the occurrence of anterograde amnesia after benzodiazepines. In terms of the model of Atkinson and Shiffrin rehearsal processes involved in transfer of information to and from LTM are disrupted after diazepam and these may explain deficits in immediate recall. Deficits in long term effects might in addition be explained by deficits in coding or impaired consolidation.

CHAPTER 8

THE RELATION BETWEEN THE DIAZEPAM-INDUCED LEVEL OF VIGILANCE AND COGNITIVE PROCESSES.
DISCUSSION AND CONCLUSIONS

8. The relation between the diazepam-induced level of vigilance and cognitive processes

The main purpose of this thesis was to establish the source of the amnestic effects of diazepam. More specifically, it was investigated whether the sedative effects of diazepam, which lead to a decreased level of vigilance, can also be held responsible for its amnestic effects and whether memory impairment is related to other disturbances in information processing.

Memory and attention are interdependent. Therefore, memory as well as attention processes were analysed. In the first series of experiments the relationship between a decreased level of vigilance induced by diazepam and attentional processes was studied. The second series of experiments was centered on the question whether the diazepam-induced decrease in the level of vigilance has a global or a specific effect on memory.

8.1. The subjective evaluation of the diazepam-induced level of vigilance

The subjective evaluation of the level of vigilance was used to investigate whether it might be considered as a first indicator of a decreased level of vigilance. The effects of 7.5, 10 and 15 mg of diazepam were evaluated and compared with buspirone and placebo (Chapter 3, 4, 6 and 7). For this purpose the Subjective Alertness Scale (SAS) (De Sonneville et al, 1984) was used. In order to compare the effects of diazepam with methylphenidate the Thayer scale was used (Thayer, 1986).

Subjects reported drowsiness, tiredness, a general slowing down, and sleepiness with all three doses of diazepam, compared with placebo. These signs are commonly related to a decreased level of vigilance. In contrast, buspirone at the same doses did not induce any change in subjective feelings. There was only one exception. In one experiment all three groups of subjects (the diazepam, the buspirone and the placebo group) reported a comparable decrease in vigilance (Chapter 4). It seems that in this experiment subjects did experience feelings of fatigue and tiredness. This decreased level of vigilance might be attributed to non-drug effects such as a long EEG registration, monotonous stimuli and half-dimmed light in the experimental room.

Methylphenidate (at a dose of 20 mg) induced effects opposite to diazepam (Chapter 7).

The decrease in the level of vigilance after diazepam is in line with the commonly reported subjective effects of diazepam. Differences with buspirone and methylphenidate were also reported by others (Boulenger et al, 1989; Ghoneim et al, 1984a; Heishman and Henningfield, 1991; Moskowitz and Smiley, 1982; Newton et al, 1982; Rich and Brown, 1991). A subjective evaluation can therefore be considered as the first indication of a changed level in vigilance after diazepam.

A possible dose-related effect of diazepam was not reliably established across the various experiments in this thesis. According to Chait (1993) a number of factors such as gender, current or past drug use, personality and baseline mood state, might explain a variability in describing (subjective) effects of the drug. Moreover, it is possible that without experience in subjective evaluation or previous training it is difficult for the subject to accurately grade his/her own subjective state. Different experimental situations might also differentially influence the level of vigilance and interfere with the evaluation of the drug's effects. Furthermore, the experiment in which evoked cardiac responses were registered (Chapter 3), was carried out on a population of Polish students and a translated SAS was used in this experiment. Perhaps the Polish version of the SAS scale was more sensitive than the Dutch version. Finally, the reported decrease in the level of vigilance at a dose as low as 10 mg of diazepam and the significant difference with methylphenidate and placebo measured by the Thayer scale might indicate that this scale is more sensitive than the SAS scale in obtaining a subjective evaluation of vigilance (Chapter 7).

To summarize, the subjective evaluation apparently indicates a decrease in the level of vigilance after diazepam intake. This type of evaluation might be considered as a first indicator of a reduced level of vigilance. Conclusions about a possible dose-related effect of diazepam could not be reliably obtained. Non-trained subjects might have some difficulties in describing their own drug-induced subjective state. Tiring experimental procedures could additionally influence the level of vigilance. Finally, it seems that the Thayer scale is more sensitive for drug effects than the SAS scale.

8.2. Effects of diazepam on attention processes

Attention and memory are generally considered separate but interdependent processes. If attention plays a role in comparing new information against information already known, then attention might be considered as a superordinate process of which memory is a critical component. Furthermore, memory formed by intentional and incidental learning influences the future direction of attention (O'Donnell and Cohen, 1993). Hence, in order to evaluate the

amnestic effects of diazepam it is necessary to investigate both memory and attention processes.

8.2.1. The diazepam-induced changes in a shifting process in attention indicated by saccadic reaction time

The effects of diazepam on attentional processes were measured by saccadic reaction time (SRT) (Chapter 2). SRT - the latency time of a saccadic eye movement - is related to the time it takes to make a decision about the saccade target and to decide when to produce a saccade (Fischer, 1981). A saccade between an old and a new fixation point reflects a change in a location of visual attention (Braun and Breitmeyer, 1988). The shift of visual attention to a new saccade target position can be defined in terms of a shifting process in attention. Herein three mental operations can be distinguished: 1. disengagement of attention from its current focus, 2. shift of attention to the location of saccade target, and 3. reengagement of attention in the new location (Posner, 1980).

The overall results presented in Chapter 2 show a general impairment of saccadic eye movements after benzodiazepines, e.g. an increased SRT. The prolongation of SRT and an increased percentage of slow saccades after diazepam at a dose of 5 mg was found in the gap and in the overlap paradigm. Interestingly, the increase in SRT was the same in both conditions. This implies that since the gap and overlap paradigm differ only in whether or not a disengagement takes place, the disengagement process is not disturbed by the drug. Therefore, it is concluded that diazepam does not affect the disengagement of attention, but rather one or both of the two other mental operations within the attention shifting process. Buspirone had no effect on SRT.

The locus of visual attention may also move without saccades (Posner, 1980). This implies that a shift of attention does not require a saccade towards a target. However, in order to shift one's attention to the target location, the relevant stimulus must be detected and the decision to shift attention towards the target must be made (Fischer, 1981).

Gómez et al (1995) combined a measurement of SRT with the recording of event related potentials (ERPs) in the gap and the overlap paradigm in drug-free conditions. They found that the faster saccades in the gap paradigm are correlated with an enhanced amplitude of the P300 component of the ERP. The interpretation of P300 is complex; however, its relation with a decision process is broadly maintained (Johnson, 1986). Furthermore, Donchin and Coles (1988) indicate that the P300 reaches its maximum peak at the time when the evaluation of a stimulus is completed. Based on the data of Gómez et al (1995), it seems that both a short SRT and a large amplitude of P300 may be interpreted as indicators of a fast decision process. In Chapter 4 a decrease of the amplitude of the P300 of the target stimulus in an oddball task after

intake of diazepam was reported. This is in line with findings of Ray et al (1992). The reduction of the amplitude of P300 might indicate a slower or less effective decision process. Therefore, if the locus of visual attention may move without saccades (Posner, 1980), than it might be assumed that before attention is shifted to the new location of saccade target, the stimulus should be detected and the decision to shift attention must be taken. This implies that there are three different aspects of shifting on which diazepam might act: detection, decision and shift. Based on the interpretation of the Gómez et al (1995) study it is hypothesised that benzodiazepines disrupt the decision making process. Whether or not diazepam also affects detection, shift, as well as the reengagement of the attention in the new location of the target remains to be established.

To summarize, the disengagement of attention is not impaired by diazepam. Two other mental operations in the shifting process in attention: (shift of attention to the location of the target and reengagement of attention in this place), seem to be affected by diazepam. The prolonged SRT suggests that the decision process about the detection of the target and furthermore the decision to shift one's attention, is mostly prolonged after diazepam.

8.2.2. The effect of diazepam on the signal value of the stimulus, measured by heart rate and the evoked cardiac response

The role of the diazepam-induced level of vigilance on stimulus evaluation task was investigated with heart rate (HR) and with the evoked cardiac response (ECR) (Chapter 3). This task was presented in two conditions: a cognitive condition (instruction - count stimuli) and a neutral one (Barry, 1996; Kaiser et al, 1996).

Tonic HR is relatively stable and reflects a base-line level. Discrete stimuli induce phasic changes in HR. Tonic HR is related to the level of vigilance. An inverse relation between the level of vigilance and the tonic HR is generally described in the cognitive condition; tonic HR is increased with a lower lever of vigilance (Barry, 1996; Barry and Tremayne, 1987). An ECR is related to a phasic measurement. It is a response to a stimulus, which represents a temporal variation in tonic HR and reflects momentary cognitive processes towards a stimulus (Hockey et al, 1986). The ECR is used as a potential source of information regarding both the registration of a stimulus (ECR1) and to what extent it is cognitively processed (ECR2) (Barry, 1996; Barry and Tremayne, 1987). ECR1 is characterised by an initial deceleration which may be followed by an acceleration, namely ECR2. ECR2 has been shown to be a function of increasing cognitive load and intensity of the processing allocated to the completion of the task (Barry and Tremayne, 1987; Cohen and O'Donnell, 1993).

An increase of the prestimulus tonic HR was found after diazepam at a dose of 7.5 mg

(Chapter 3). This is in line with others (Adinoff, 1992; DiMicco, 1987; Goldstein et al, 1982; Muzet et al, 1982). Due to the inverse relationship between HR and the level of vigilance, the increase in HR corresponds with a decreased level of vigilance. Buspirone reduced the prestimulus HR which may suggest a stimulatory effect of this drug. Next, there was no instruction effect upon the prestimulus HR level, suggesting that the instruction did not change the level of vigilance. The poststimulus HR showed a biphasic response to the stimulus as expected in the count condition. ECR2 was more apparent in the count than in the neutral condition. These outcomes are in line with results from Barry et al (1996) and Kaiser et al (1996). There was a clear drug effect on the two components of the ECR. ECR1 was enhanced after diazepam and reduced after buspirone intake. However, it appeared from the analysis of covariance that the changes of ECR1 induced by both drugs were dependent on the drug induced changes of prestimulus HR. In contrast, ECR2 was not influenced by drug effects on prestimulus HR. Furthermore, buspirone enhanced and diazepam reduced ECR2. This demonstrates facilitatory effects of buspirone and a decrease of cognitive processing after diazepam. It seems that the decrease of ECR2 found after diazepam is due to a reduced engagement of the subjects in the task. The reduced ECR2 after diazepam may be regarded as a cognitive-motivational neutralization of the signal value of the stimulus.

To summarize, diazepam enhances and buspirone reduces tonic HR. The enhancement of HR after diazepam may indicate a decreased level of vigilance. The effects of the drugs on ECR1 are dependent, and on ECR2 independent from changes in tonic HR. Diazepam reduced the acceleration of ECR2. Such a decrease suggests a reduced process of attentional engagement of the subjects in the task leading towards a reduced cognitive-motivational processing of the stimulus. Buspirone reduced HR and enhanced acceleration of ECR2, which may indicate that this drug increases the level of vigilance and facilitates the elaboration of the meaning of the stimulus.

8.2.3. Stimulus evaluation after diazepam measured by event related potentials

The question whether a decrease in the level of vigilance induced by diazepam reduces cognitive processes as measured by event related potentials (ERPs) was addressed in Chapter 4. This relationship was investigated in an experiment in which stimuli were presented under a neutral instruction and also in a classical oddball paradigm. This allowed us to make two comparisons. The first comparison is between ERPs produced by standard stimuli of the oddball task and identical stimuli under a neutral condition. According to García-Larrea et al (1992), this comparison can indicate changes in the level of vigilance between the two stimulus conditions since it can be assumed that the subjects' involvement in the oddball task is larger

than in the neutral part. The second comparison is between ERPs elicited by standard and target stimuli in the oddball task. The P300 elicited by target stimuli is generally larger with more positivity in comparison with the P300 elicited by standard stimuli (Donchin and Coles, 1988; Ruchkin et al, 1980a, Ruchkin et al, 1988; Verleger, 1988). The amplitude of the P300 is assumed to be proportional to the degree of updating memory representation in the context in which the stimulus is presented (Donchin and Coles, 1988). Moreover, the amplitude of P300 is proportional to the efficiency of the decision process (Johnson, 1986). Generally, no late components except the P300 are reported under drug conditions. We found some indications for a late slow positive component which could occur until 1000 msec after stimulus onset. The late slow wave positivity which followed the P300 (>500 msec) is considered an indicator of additional efforts involved in the categorisation of stimuli and can be enhanced with increasing task demands (Ruchkin et al, 1980a, Ruchkin et al, 1988). In both comparisons the analysis was made in two post-stimulus epochs. The first (250-574 msec) included the P300, while the late slow wave positivity was reflected in the second window (576-900 msec).

In the analysis of ERPs in both comparisons emphasis was laid on the amount of positivity. The amount of positivity is defined as a positively deflected surface of ERPs in a chosen time epoch.

The difference score of the first comparison suggests that that there was a significant amount of positivity in both windows in the placebo and buspirone group, but not in the diazepam group. The lack of positivity after diazepam might imply that the level of vigilance is not enhanced as it can be predicted from the work of García-Larrea et al. (1992). This suggests that the subjects' involvement in the oddball task was not higher than under neutral stimuli presentations. In contrast, the positivity in the buspirone and the placebo group indicates that they are more involved in the oddball task and that the level of vigilance might be increased.

The between-group analysis showed a clear drug effect for positivity in the first window: there was more positivity in the buspirone than in the diazepam group. In all, the data suggest that overall vigilance was decreased after diazepam and enhanced after buspirone. The enhancement of the level of vigilance suggests a stimulatory effect of buspirone. Interestingly, the subjective evaluation of level of vigilance indicates a comparable decrease in the level of vigilance in all three drug conditions. It suggests that the tiring procedure of the experiment increased fatigue in all groups, but had no effect on the involvement in the oddball task in the buspirone and the placebo group. It also demonstrates that objective measures are more sensitive for drug effects than subjective reports.

The second comparison was done in the classical oddball task. Under the placebo condition, a regular difference between two stimuli of the oddball task was found in the first window. In agreement with many others, the target stimulus elicited more positivity than the

standard stimulus (Duncan-Johnson and Donchin, 1982; Johnson, 1986; Pritchard, 1981). This difference was reduced after diazepam (marginally significant), suggesting that the amount of cognitive effort was reduced. Surprisingly, this difference was not significant in the buspirone group and this might suggest that even less effort was invested by the subjects under this drug. However, no difference in the amount of positivity was found between drugs, suggesting that the within group differences are not robust. There were no significant differences in the second window, reflecting late slow wave positivity.

A separate analysis of the amplitude of P300 after target stimuli indicated that this component was reduced after diazepam and increased after buspirone. The effects of diazepam suggest that context updating and decision processes about detection of target stimuli are impaired. The enhanced amplitude of P300 and the large positivity in the first and second window in the first comparison indicate that buspirone does not impair cognitive processing or have, even opposite, stimulatory effects. Generally, more positivity was found after the target stimuli that after the standard stimuli. Therefore, it seems that both target and standard of the oddball task were equally elaborated in the buspirone group. It is suggested that not only context updating and decision processing of target stimuli but also processing of standard stimuli are facilitated in the buspirone group. The updating process might involve a 'marking' of some features of an event, in our case the target stimulus, in order to make this event 'distinctive' from the standard stimulus (Coles et al, 1990). Therefore, the reduced amplitude of P300 after target stimuli apparently indicates that less benefit is gained from the repeated stimulus presentations in the diazepam group. It seems that recognition of the target and standard stimuli is less facilitated by context updating after this drug. It might even be possible that reduced context updating contributes to a decrease in the consolidation process. An impaired quality of these processes is uncovered by an increased number of omissions of the target detection and by an increased RT.

In all, the placebo data suggest that late slow positivity was most clearly revealed from comparison one and not from comparison two. It was thought that the difference between the target and standard stimuli might have been too large in order to obtain significant amounts of positivity in the second window. Another reason for investigating late slow wave positivity originates from the work of Ruchkin et al (1980a). They suggested an inverse relation between late slow wave positivity and accuracy. Therefore, late slow wave positivity was more closely investigated in a drug-free experiment in which the level of difficulties was manipulated (Chapter 5). A larger amount of late slow wave positivity was to be expected if the differences between target and standard stimuli were small. Next, the effect of a motor response towards the target stimulus was investigated. The instruction to respond might also enhance the cognitive load and influence the P300 and perhaps also late slow wave positivity.

Oddball tasks were presented to the subjects twice (with and without a requirement to make a motor response), whereas the discriminability between standard and target stimuli was also varied. Target stimuli with a motor response elicited more positivity than target stimuli without motor response in the first window. In the second window the effect of the level of difficulty by decreasing the discriminability was significant. Reaction time of the motor response was enhanced with an increased level of difficulty. In the other words, the ERP data suggest that positivity in the first window is sensitive for the motor response and in the second window for the level of difficulty. It is of interest that the level of difficulty was without any effect in the comparison between neutral and target stimulus, whereas the execution of motor response yielded significantly more positivity in the first window.

The data in Chapter 5 indicate that a motor response has a large effect on the amplitude of the P300 associated with an effect on the amount of positivity in the first window. Therefore, by relating the data of the drug-free experiment to the evaluation of diazepam effects on ERPs, it can not be excluded that the instruction to press a button towards a target under drug conditions can obscure or interact with the drug effects as reported in Chapter 4. On the other hand, it might be that the diazepam-induced decrease in P300 has been caused by a decrease in the quality, speed, and accuracy of the required motor response. So, it would be interesting to compare the effects of the drug in the oddball task with and without a motor response. The lack of positivity in the second window in the same comparison in Chapter 4 indicates that the oddball task was equally easy for all groups and that no additional efforts to evaluate stimuli were necessary under drug conditions. Aside from this, it is suggested that late slow wave positivity is more sensitive to the reduced accuracy in responding towards stimuli due to the level of difficulty in the task, than to the prolonged RT towards target stimuli in the oddball task.

To summarize, the positivity found in the first comparison suggests that subjects are more involved in the oddball task than in the neutral task, they seem to be more vigilant and active. The lack of positivity in the diazepam group suggests that the level of vigilance was not increased and the subjects' involvement was not changed by the instruction to discriminate the stimuli as was the case in the buspirone and placebo group. Furthermore, the between group analyses revealed contrasting effects of diazepam and buspirone on early positivity. This is interpreted in a sense that diazepam decreases and buspirone increases the level of vigilance. Diazepam reduced the amplitude of P300; it seems that the context updating process or the decision processes on target stimuli are impaired. This is also confirmed by an increased number of omissions and an increased RT of motor responses.

Slow wave positivity is found in the first and second window, mainly at Pz. Slow wave positivity in the second window is related to the level of difficulties and inversely related to

accuracy of the motor response. Motor responses have an effect on positivity in the first window. Neither of the manipulations influenced positivity in comparing the neutral and the target stimulus. Finally, it cannot be excluded that drug effects are obscured by the instruction to make a motor response.

8.2.4. The neuropsychological approach for changes in attention and concentration induced by diazepam

Attention and concentration were evaluated with the Bourdon-Vos test, the trail making test and a simple auditory reaction task (Chapter 6). The effects of diazepam at a dose of 15 mg - an impairment of performance - were clear in all tests. In the Bourdon-Vos test a prolonged time necessary to finish the test was found as well as a deficit in accuracy indicated by an increased number of omissions. A prolonged time necessary to complete the task was present in A and B part of the trail making test. The performance in the simple auditory time task was slowed down. Buspirone had no effects on performance in any of these tests.

All tests were performed with the dominant hand. Results discussed in Chapter 6[7] indicate that the use of the preferred hand can compensate for the muscle-relaxant properties of diazepam. Therefore, the impaired performance of all attention and concentration tests probably does not result from the muscle-relaxation properties of the drug. Interesting results were found when the Bourdon-Vos test was divided into three parts and these parts were analysed separately. There was no drug effect in the first two parts, however, in the third part a significant prolongation of the time necessary to complete that part was noticed after diazepam intake. It seems that the impairment of attention and concentration might occur gradually or possibly be compensated in the first parts of the test. However, this compensation did not last very long and the performance was decreased in the last part of the task. The accuracy deficit on the contrary, was present in the entire test.

Overall, it is concluded that the performance of short, easy or entertaining tasks under the influence of benzodiazepines is not impaired, most probably due to temporary enhanced attention (Hart et al, 1976; Kleinknecht and Donaldson, 1975; Koelega, 1989). However, attention seems to drop over time. A decrease of performance level in the trail making test was present in part A and B, but not in part C of the test. Part C is comprised of items from parts A and B of the test. This may suggest that variability of items temporarily enhances attention and concentration in this part of the task. A prolongation of reaction times in the simple auditory

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[7] Effects of diazepam on motor performance are described in the paragraph (/8.3./). In this paragraph the differences between motor performance with the preferred and non-preferred hand are extensively discussed.

reaction time task was found after diazepam, in agreement with previous results (Kleinknecht and Donaldson, 1975; Koelega 1989). These subjects needed more time to respond towards tones.

To summarize, decreased attention and concentration emerged from all tests. Interestingly the performance deficit in the Bourdon-Vos test was found in the final part of the test and in the trail making test in the first two parts of the test, suggesting impairment of sustained attention. An assumed temporary enhancement of attention in the short, easy or entertaining tasks after diazepam might explain the lack of effects of diazepam in the first two parts of the Bourdon-Vos task and in the last part of the trail making test. Buspirone had no effects of the performance of attention and concentration tests.

8.3. Effects of diazepam on motor performance

Motor performance was measured in order to determine whether the increase of reaction time after 15 mg of diazepam is due to impaired motor performance (Chapter 6). Motor performance was tested by the peg board, by finger tapping and by an auditory simple reaction task. In all tasks speed was the denominator of performance.

Motor performance was decreased in all three tests after diazepam. Others have also found increased movement times (Kleinknecht and Donaldson, 1975; Peck et al, 1976; Peck et al, 1977; Roth et al, 1977; Roth et al, 1979). The increased response time and decreased number of taps was found to be dependent on the use of the preferred or non-preferred hand. The drug effects were most pronounced when the non-preferred hand was used. Buspirone had no effects on motor performance. Generally no distinction was made between the preferred and the non-preferred hand in the literature. From the present data it becomes clear that measurement of the performance with the non-preferred hand is more effective in indicating an impairment after diazepam than with the preferred hand. This is not only true for the peg board task in which extensive manual movements (lifting and replacing a small wooden block) is required, but also when micro-movements (tapping) are asked for. Lack of direct impairment with the preferred hand after diazepam might indicate that the muscle relaxant effect can partly be compensated by the use of the preferred (dominant) hand. For future research towards muscle relaxing properties, it might be interesting to test the performance with the preferred and the non-preferred hand.

Increased reaction times were found in the simple auditory reaction time task after diazepam, suggesting that execution times were prolonged by the drug. However, a simple auditory reaction time task involves, besides execution time, attention and concentration as well. The results of the auditory simple reaction task were therefore discussed in the paragraph on

attention and concentration (/8.2.4./). Since performance was measured on the preferred hand, it may be concluded that it is not likely that muscle relaxation is causing the increase in the execution time. Since the Bourdon-Vos and the trail making test were performed with the dominant hand, this conclusion can be also extended to performance in these tests.

To summarize, the results of motor performance tests suggests that muscle relaxant properties of diazepam, especially when the non-preferred hand is used to perform the task, result in impaired performance. Buspirone did not influence the performance of psychomotor tests.

8.4. Effects of diazepam on memory

In two experiments the effects of 10 and 15 mg of diazepam on short (STM) and long term memory (LTM) were evaluated. They were respectively compared with 20 mg methylphenidate (Chapter 7) and 15 mg buspirone (Chapter 6). The comparison of the effects of diazepam with buspirone was made in order to investigate whether sedation, or the decreased level of vigilance, plays a major role in memory impairment. The comparison of the effects of diazepam with methylphenidate was made in order to investigate the relation between vigilance and memory. Diazepam decreases and methylphenidate increases the level of vigilance. It was thought that if anterograde amnesia is indeed induced by the sedative properties of the drug, a drug with an opposite action on vigilance might facilitate memory.

The effects of diazepam on memory - anterograde amnesia and retrograde facilitation - will be discussed in Section 8.4.2. and 8.4.3. respectively. The relation between amnestic effects of diazepam and a decreased level of vigilance will be described in Section 8.4.4.

8.4.1. The memory model of Atkinson and Shiffrin

The model of Atkinson and Shiffrin (1968 and 1971) is often used in drug research (e.g. Curran, 1986; Ghoneim and Mewaldt, 1990; Lister, 1985). There are three general memory components in this model: sensory memory (SM), short term memory (STM) and long term memory (LTM). SM is the component that receives auditory and visual stimulation from the external environment. STM can be considered as a memory register which holds current information. LTM is a memory component where information is stored on a relatively permanent basis and has a large capacity. The capacity of the STM is limited to 7-9 items and the retrieval from STM might only be possible in a limited time (15-30 sec). STM not only receives information from SM but also from LTM. Information retrieved from LTM enters STM and is further recalled from this memory buffer. The retrieval from LTM requires selection of

certain information as a 'probe information' that is placed in STM. The 'probe' activates a 'search set' in LTM which is closely associated with the 'probe'. The activated 'set' is put in STM and examined for the desired information. If it is not found, search is stopped or started again with a new 'probe'. There are some processes involved in the control of transfer of information from STM to LTM, such as rehearsing and coding. Moreover, decision rules, organisational schemes and retrieval strategies are involved in the control of transfer. Rehearsal, the most important control process, maintains information in STM and, at the same time, transfers information from STM to LTM. If a number of items is presented, successive items enter STM until the maximum number is reached (maximum capacity). Thereafter, each new item which enters STM replaces one of the items being already in STM. The strength of the LTM memory trace seems to be a function of the length of time an item resides in the rehearsal buffer; the longer the time, the more rehearsal the item receives and therefore the better the transfer into LTM is. Next, the learned information is better stored in LTM when the rehearsal is combined with coding than without coding. Coding is a control process in which the item to-be-remembered is put in a context of additional information from LTM and then rehearsed as an entire complex in STM. These control processes are optional. They may vary in different tasks. Therefore, the amount and efficiency of rehearsals contribute to a better storage of items in LTM. A factor improving the quality of storage of information in LTM is consolidation, a kind of coding process which also takes place in LTM. During consolidation each learned item is encoded into a richer memory representation including any extra information about the item-to-be-remembered. This additional information encoded along with the learned item may be considered as cue increasing the accessibility of the remembered item for its retrieval (Ashcraft, 1989; Atkinson and Shiffrin, 1968; Atkinson and Shiffrin, 1971).

Although attention is a fundamental feature of human information processing, nothing in Atkinson and Shiffrin's model is labelled explicitly as attention, and there is no component that encompassed attention. However, attention can be considered as an interacting or supervisory process rather than as a structural component of memory. Therefore, attention does not have a well circumscribed position in the model (Ashcraft, 1989). It is suggested that attention may be referred to as processes controlling the selection of information passing into and out of STM and LTM (O'Donnell and Cohen, 1993) and therefore, attention might interact with performance in both STM and LTM tasks.

8.4.2. Amnestic properties of diazepam: short or long term memory?

A dose of 15 mg of diazepam and buspirone were given in the first experiment (Chapter 6). STM was investigated with the digit span test. The word fluency test, the immediate and

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delayed recalls of the 15-word test as well as the complex figure test were used to evaluate LTM. Diazepam affected only the backward recall in the digit span test and all the tests measuring LTM except the word fluency test. The impairment of the delayed recall of the words of the 15-word test and the reproduction of the complex figure test was present in the post-drug session as well as during the evaluation one week later. Buspirone did not influence the performance of any of these tests.

In the second experiment 10 mg diazepam was compared with 20 mg methylphenidate (Chapter 7). The 15-word test was used to evaluate LTM. The recall of the fifth immediate and the delayed recall of the 15-word test were impaired after diazepam. Methylphenidate did not influence any of the recalls in the 15-word test. The data of the 15-word test were analysed in more detail with respect to the recall of the first (primacy) and the last three words (recency effect). Diazepam reduced the recall of the first three words at the first immediate and the delayed recall, but not at the fifth immediate recall. The recall of the last three words was affected by diazepam only at the delayed recall. The amount of forgetting as measured in the delayed recall after diazepam tended to be greater for the first three than for the last three words.

In line with others it was found (Chapter 6) that the (forward) recall of the digit span test was not impaired by diazepam (Brown et al, 1982; Jones et al, 1978). As a consequence, all processes preceding STM, including input to the SM and transfer from SM to STM, were well preserved after diazepam intake. The obtained impairment in the backward recall of the digit span test is interesting. In order to recall the series of digits backward, it is not only necessary to remember the forward series but also to create a new one in a reversed order. If the subject creates a reversed series, than it might be possible that he has to remember two series of digits, the old and the new one. Considering the limited capacity of items into the STM, some digits are temporarily transferred to the LTM. Hence, it is proposed that this transfer from STM to LTM is vulnerable to benzodiazepines. This suggestion is in agreement with conclusions from several reviews (Curran, 1986; Ghoneim and Mewaldt, 1990; Lister, 1985).

A slightly more precise and relevant to the model explanation can be given for the data from the 15-word test. Here the number of items is also larger than the capacity of STM. Therefore, transfer to and from LTM is necessary for a proper recall of the words. According to the model, the number of rehearsals is related to the quality of the immediate and delayed recall. In addition, the quality of the delayed recall also depends on the coding process in the STM and the consolidation process in the LTM. The poor recall after diazepam suggests that these processes are also impaired by the drug.

If the number of items becomes larger than 7, the most recently presented items are relatively safe and well remembered (Jones et al, 1978). They stay in STM. In agreement with this, a tendency was found for the first three items of the 15 words to have a higher sensivity to

be forgotten than the last three words. These last few items are not transferred, they stay in the STM and therefore are more often rehearsed and less vulnerable to diazepam intake. A second argument for a role of rehearsals in explaining the amnestic effects of the diazepam is the fact that the first three words were already impaired in the first immediate recall after diazepam. Interestingly, the first three words in the fifth immediate recall were not impaired after diazepam. Although a rehearsal might be less efficient, a ceiling effect at the fifth immediate recall was found and this might obscure putative drug effects. Similar to the interpretation of the data of the 15-word test, the deficit in the complex figure test might be due to less appropriate coding or impaired consolidation.

In a pilot study (similar in design as the experiment described in Chapter 7) effects of diazepam were found in another type of verbal long term memory test - a paired association word test. Here the recall of unrelated words was more impaired than the recall of related words and this difference was stronger after diazepam. Gorissen et al (1995) found that related words in a semantic priming task were better recalled and that unrelated words were more vulnerable to the effects of benzodiazepines. Related words already have a certain associative strength, or, their semantic content overlaps (i.e. bread - butter). It is assumed that the association between related words already exist and is already so strong that there is no need to form new ones. The semantic content between words in the related pairs seems to facilitate the coding and consolidation process. Anterograde amnesia for the unrelated words might be due to difficulties in forming new associations. Another possibility is that the unrelated words are less accessable for a correct recall than related words (Gorissen et al, 1995).

The recall of information (already stored before the experiment) as measured in the word fluency test, and tested after the drug intake, is not impaired after diazepam (Chapter 6). Next, the recall of the related words was less impaired than the recall of unrelated pairs (the pilot study). The outcomes of both tests indicate that diazepam does not impair the retrieval of information learned before the drug intake nor the recall of related words after the drug intake (Curran, 1986; Ghoneim and Mewaldt, 1990; Lister, 1985).

The phenomenon of state-dependency is often used to explain drug induced anterograde amnesia (Overton, 1978). Evidence for a state-dependent learning or rather recall[8] after benzodiazepines appears conflicting (for review see: Curran, 1986; Lister, 1985). A discrepancy in reported occurrence of state-dependent learning is due to the methods used to obtain the retrieval (Brown et al, 1982; Eich, 1980; File and Lister, 1983; Lister and File, 1984;

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[8] It seems that it would be more correct to use the name of state-dependent recall or retrieval rather than state-depending learning. The state-dependency recall describes a phenomenon in which the retrieval of information is impaired due to the fact that subject is in a drug state different than that in which the information was learned. It is supposed that if the original state is reproduced no impairment occurs (Lister, 1985).

Lister, 1985). A state-dependent effect is generally noticeable when a free recall is required, while no state-dependent results are reported when retrieval is assessed using recognition tests or when a cue is provided. In Chapter 6 and 7, anterograde amnesia is reported in the free recall of the 15-word test and in the cued recall of the word pairs (the pilot study). A strong argument against the state-dependency hypothesis is that amnestic effects of benzodiazepines are also found in the one-week-later-evaluation session. During the evaluation, subjects were no longer under the influence of the drug. Hence, it is felt that state dependency does not play a major role in the amnestic effects induced by diazepam.

To summarize, SM, the acquisition to STM from SM as well as the retrieval from LTM are not impaired after diazepam. The transfer and consolidation seem to be affected by diazepam. In terms of the Atkinson and Shiffrin's memory model, it is suggested that the rehearsal providing transfer of information to LTM is impaired: this can be either the number of rehearsals or the efficiency of rehearsals. The strength of associations between related words might prevent the occurrence of anterograde amnesia. Memory impairment of unrelated words might be due to decreased possibilities to form new associations or reduced accessability of these words in LTM. State-dependency is not likely to play a major role in the amnestic effects induced by diazepam described in this thesis.

8.4.3. Retrograde facilitation after diazepam

One week after the pre-post experiment the performance on the memory tests was once more tested in the evaluation session (Chapter 6). No drug was administered during this session. Clear facilitatory effects (retrograde facilitation) on the performance in the complex figure test were found in the diazepam group. The material learned prior to drug intake was better remembered in the diazepam than in the buspirone and placebo group. Considering the fact that retrograde facilitation was found in the one-week-later-evaluation session, it seems that state-dependency can not be used to explain this effect on memory. There was no such an effect for the verbal material of the 15-word test. Coenen et al (1989) also found evidence for retrograde facilitation for the complex figure tests and not for the 15-word test during a one-week-later-evaluation session. This indicates that the complex figure test is more sensitive for diazepam effects.

The phenomenon of retrograde facilitation is poorly understood. However it is sometimes reported that concurrent with anterograde amnesia, the number of pre-drug presented words recalled after drug intake was increased (Ghoneim et al, 1984a). Therefore, it seems that retrograde facilitation is somehow related to the amnestic effects of the drug. A reduced number of items remembered after drug intake reduces the number of interferences with the pre-drug

learned material and this may suggest a cause-effect relationship between number of interferences and forgetting (i.e. Ghoneim and Mewaldt, 1990; Hinrichs et al, 1984).

The lack of clear retrograde facilitation in the 15-word test suggests that the greater number of items to-be-remembered in the complex figure test than in the 15-word test, plays a role. Also a difference in the modality of the presentation of items might explain this discrepancy. In agreement with Jones et al (1978) and Linnoila (1984) it is suggested that visual items to-be-remembered seem to be more sensitive for diazepam than verbal items.

To summarize, diazepam might facilitate the recall of items learned just before the drug intake. Retrograde facilitation is not state-dependent and can be easily found in an evaluation session one week later. Retrograde facilitation might be explained as a secondary effect of anterograde amnesia and might be related to a reduced number of interferences between the pre- and post-drug learned material. A smaller number of interferences results in a decrease in the number of items forgotten.

8.4.4. The relation between amnestic effects of diazepam and the level of vigilance

The anxiolytic diazepam induces amnesia, sedation, and it decreases the level of vigilance. The data from the experiment comparing the effects of diazepam and buspirone on memory (Chapter 6) indicate that this memory impairment is not caused by the anxiolytic actions of diazepam but rather by its sedative effects. The reported lack of performance impairment on a memory test after clobazam (a benzodiazepine with less sedative effects) might also indicate that anterograde amnesia is due to a reduced level of vigilance rather than to the anxiolytic properties of benzodiazepines (Alford et al, 1991; Hindmarch, 1995). However, there are two arguments which do not favour the hypothesis that the amnestic effects are caused by a decrease in vigilance.

First, methylphenidate did not improve the recall in a verbal memory test while the subjective level of alertness was increased (Chapter 7). Although not many studies were undertaken to examine memory under influence of methylphenidate, the data in Chapter 7 are in agreement with the few available studies i.e. by Aman et al (1984) and Wetzel et al (1981) who reported that the performance in the short term memory tests was affected by this drug, but not the performance in verbal long term memory tests. It is necessary to underline here that it is difficult to increase the level of vigilance with methylphenidate in fully alert and healthy subjects. The second argument originates from an experiment in which two ways to reduce vigilance, sleep deprivation, and diazepam administration were compared. It was found that the diazepam-decreased level of vigilance was accompanied by anterograde amnesia whereas the

reduced level of vigilance by sleep deprivation was not (Coenen and Van Luijtelaar, 1997; Gorissen et al, 1997). However, the non-pharmacologically reduced level of vigilance differs from the diazepam-decreased level of vigilance: the sleep deprived subjects were less alert and more tired, depressed, angry, and fatigued than subjects from the diazepam group (Gorissen et al, 1997). Furthermore, the experiment with the sleep deprived subjects began after 24 hours of being awake, and with those to whom diazepam was administered approximately 60 min after drug intake. So, the duration of being awake may be one of the factors causing the difference between both types of reduction in level of vigilance. In all, the diazepam-reduced level of vigilance might be difficult to compare with the non-pharmacologically reduced level of vigilance.

The reduced level of vigilance after diazepam was, besides subjective reports, also expressed in a increased prestimulus tonic heart rate (HR) (Chapter 3). This, in combination with a reduced acceleratory component of the evoked cardiac response (ECR2), might indicate that the engagement in a task is reduced after diazepam, leading towards a cognitive-motivational neutralisation of the signal value of the stimulus. The ERP data suggest that the involvement in the oddball task was not increased after diazepam, in contrast to what happened in the two control groups (Chapter 4). Therefore, it is supposed that the diazepam-induced level of vigilance might play a certain role in the reduction in the subject's interest in a stimulus or engagement in a task. The slowing down of the saccadic reaction time was another clear effect of diazepam, which was interpreted as a decrease to shift one's attention (Posner, 1980; Posner et al, 1987) or the decision to shift (Chapter 2). Whether and how these physiological data and the neuropsychological data suggesting a decrease in attention, can be held responsible for the amnestic effects needs further evaluation. It might also be interesting to compare the effects of diazepam on HR and ECR2 as well as on ERPs with the effects of sleep deprivation. This in order to investigate whether and how attentional and other cognitive variables are differentially affected by the two procedures of inducing a low level of vigilance.

Considering all arguments, it seems that the relation between the diazepam-reduced level of vigilance and anterograde amnesia is not clear. Rather clear, however, is a decrease of performance in the memory test and a decrease in the level of vigilance after diazepam and correlation coefficients suggesting a weak relationship between recall and alertness. Impaired attentional processes might disrupt information processing and cause memory impairments. King (1989) also does not reject in general the role of vigilance in anterograde amnesia after diazepam. On the contrary, he suggests that the diazepam-induced level of vigilance might be a secondary factor disrupting memory.

To summarize, the association between vigilance and memory is yet not clear. The lack of the effects of buspirone and clobazam on memory in comparison with diazepam suggests that

the sedative effects of diazepam but not its anxiolytic properties play a role in the diazepam-induced memory impairment. On the other hand, the lack of influence of methylphenidate on memory and the sleep deprivation data indicate that there is no direct and simple relation between vigilance and memory. Reduced alertness might explain, to a small extent, the amnestic effects.

8.5. The influence of buspirone on cognitive processes

It is generally reported that buspirone does not induce any cognitive impairment in comparison with placebo (Boulenger et al, 1989; Goldberg and Finnerty, 1984; De Maio, 1988). In line with this, no effects of buspirone on saccadic reaction time (SRT) (Chapter 2) nor in the performance of attention and concentration and psychomotor tests (Chapter 6) were found.

Buspirone decreases the prestimulus heart rate (HR) (Chapter 3). This result is at variance with previously reported findings that buspirone does not influence tonic HR (Goa and Ward, 1986; Tyrer et al, 1985). Although this discrepancy needs further evaluation, this difference might emerge from the fact that in both mentioned studies the general tonic HR was measured for a certain time whereas in this thesis the prestimulus tonic HR was registered in the task situation only during a few seconds preceding a stimulus. The discrepancy between the present and earlier data might indicate that in the rest and/or the alert situation HR is not changed and in the task situation HR is reduced after buspirone. Because of an inverse relation between the level of vigilance and the prestimulus tonic HR (Barry, 1996), the decrease of HR after buspirone suggests stimulatory effects of the drug. Buspirone also induced a larger acceleratory component of evoked cardiac response (ECR2), relative to that which occurred under placebo condition. This is interpreted as an increased engagement in the task and again suggests a stimulatory effect of buspirone. Moreover, the enlarged ECR2 might be interpreted as an increased cognitive load and an increased intensity of the processing allocated to task completion (Barry and Tremayne, 1987; Cohen and O'Donnell, 1993).

The recall in the verbal memory test (the 15-word test) but not the recall in the visual test (the complex figure test) was impaired in the evaluation session one week after the experiment (Chapter 6). During the post-drug part of the experiment buspirone had no effects on performance in all memory tests. This discrepancy in modalities of the presented items to-be-remembered as well as the fact that this impairment was obtained only during the evaluation one week after the experiment needs further evaluation.

Standard stimuli of the oddball task elicited more positivity in the first window than the same stimuli did under neutral conditions. This positivity was larger in the buspirone than in the

diazepam group (Chapter 4). The enhancement of the positivity might suggest that the level of vigilance was increased due to a higher involvement in the oddball task in the buspirone group. The amplitude of the P300 elicited by target stimuli of the oddball task was also larger after buspirone than after diazepam, but it was not different from placebo. Considering the common interpretation of P300, the data suggest that cognitive processing, context-updating and the decision process related to the target stimuli in the oddball task were not impaired by buspirone.

To summarize, buspirone has no influence on the performance of attention and concentration tests, psychomotor tasks nor on SRT. Moreover, buspirone does not influence the performance of memory tests during the post-drug session. The impairment of recall of the post-drug learned verbal but not visual material obtained in the one-week-later evaluation session underlines the modality difference which was also found after diazepam. Effects of buspirone on HR and ECR2 indicate an increased level of vigilance and facilitation of the elaboration of stimuli. The data obtained in the ERP experiment after buspirone suggest a minor increase in the involvement in the oddball task as well as in the level of vigilance.

8.6. Final conclusions

The benzodiazepine diazepam induces anterograde amnesia and retrograde facilitation. Sensory memory (SM), acquisition of information to short term memory (STM), and retrieval of information were not impaired after diazepam. The coding processes in STM, the transfer of information from STM to LTM by rehearsals and consolidation in LTM seem to be affected by the drug. A strong association between words might facilitate a coding process and facilitates recall. The difference between STM and LTM is striking: it might be speculated that newly presented items from a list to-be-remembered may dislodge items currently in STM, leading to displacement of items from STM to LTM. During the latter process the items become vulnerable to diazepam intake.

For retrograde facilitation the modality and number of items seem to play a role. The amnestic effects could not easily be explained by state-dependency. The delayed recall is more sensitive for diazepam effects than the immediate recall.

A reduced level in vigilance due to the sedative properties was expressed in an increase in saccadic reaction time (SRT), tonic heart rate (HR), event related potentials (ERPs), and in subjective alertness. A subjective evaluation may be considered the first indicator of a reduced level of vigilance. The Thayer scale seems to be more sensitive to indicate diazepam-induced levels of vigilance than the Subjective Alertness Scale (SAS) is. Buspirone may have some stimulatory effects. From a comparison between the sedative drug - diazepam - and the non-sedative drug - buspirone - on memory, it became clear that the reduced level of vigilance after

diazepam but not its anxiolytic action contributes to the diazepam-induced memory impairments. An enhancement of the level of vigilance by the drug methylphenidate did not improve the performance in memory tests. This weakens the assumed relation between vigilance and amnesia.

Motor impairments could be more easily detected if the non-preferred hand was used. Diazepam induced, besides amnesia, also cognitive impairments as was revealed by the outcomes of several neuropsychological tests and some psychophysiological variables. Impairments were found on attentional processes, decision processes, elaboration of stimuli, and task involvements although compensatory processes might obscure the detoriations. Slowing down of attentional processes indicated by SRT and performance of attention and consolidation tests might reduce the quantity as well as the speed of rehearsals. It might be speculated that newly presented items from a list to-be-remembered may be rehearsed too slowly. This may lead to their dislodgement and displacement during transfer from STM to LTM. Whether and how other effects are involved or interact with the amnestic effects, needs to be elucidated. However, it might be possible that these impairments may have an effect on the efficiency of the rehearsal and consolidation process.

8.7. Suggestions for further research

The relation between vigilance and amnesia is not clear. In order to evaluate the relation between vigilance and memory performance and to obtain an effect of an increased level of vigilance after methylphenidate, it is suggested that methylphenidate intake should follow diazepam administration or the sleep deprivation procedure.

Little is known about the circumstances under which retrograde facilitation occurs. In order to investigate under which condition retrograde facilitation for verbal memory tests can be obtained, it is suggested to vary the interval between the experimental and the evaluation session and the amount of items to-be-remembered.

Prevention of amnestic effects can be extremely important considering the large number of chronic benzodiazepine users. We have some indications that the stimulus modality is important. In order to test whether the impairment on the performance of memory tests depends on the modality of the presented stimuli, it is suggested to compare the recall of the 15-word test presented verbally and visually.

One of the mnemonic techniques can be based on the formation of associations of items to-be-remembered. It is therefore proposed that one should examine the difference between a free and a categorised recall of a 15-word test as well as a free and a cued recall of other types of memory tests (i.e. a paired associated test).

It is not yet tried to differentiate between the efficiency of the rehearsal process and/or the coding process. In order to evaluate the quality of rehearsals it is suggested that one should manipulate the rate of presentation of items to-be-learned. In order to test the role of coding processes it is proposed that one should manipulate the instruction to code and to compare the free, categorised, and cued recall.

The data from Chapter 5 indicate that a motor response has a major effect on the positivity in the first window. In order to investigate whether a motor response obscures or jeopardizes possible drug effects, it might be interesting to repeat the oddball task with and without a motor response.

SUMMARY

The central theme of the thesis is centered on the question whether sedative effects of diazepam, leading to a decrease in the level of vigilance, can be held responsible for the drug induced memory impairment in humans and whether diazepam-induced memory impairment is related to other disturbances in information processing. The effects of diazepam (Valium® - an anxiolytic drug with sedative effects) were compared with the effects of buspirone (Buspar® - an anxiolytic drug without sedative effects) in order to evaluate whether effects of diazepam on cognitive processes are related to the drug-induced decrease in vigilance or to the anxiolytic actions of the drugs. Next, a comparison between diazepam and methylphenidate (Ritalin® - a stimulant drug) was made in order to investigate further the relationship between vigilance and memory. Memory and attention are considered as interdependent processes. Hence, in order to evaluate the amnestic effects of diazepam, both memory and attention processes were investigated.

Chapter 1 introduces the term 'vigilance' and methods of its measurement. Next, tests measuring performance (memory, attention and concentration as well as motor performance), subjective states and physiological variables such as saccadic reaction time (SRT), heart rate (HR), evoked cardiac responses (ECR) and event related potentials (ERPs) are introduced in this chapter. All physiological variables are characterised in the scope of paradigms in which they can be measured; furthermore their parameters are discussed in relation to cognitive processes. Moreover, the administered drugs (diazepam, buspirone and methylphenidate) are described with respect to their action and possible side-effects.

The experiment described in **Chapter 2** evaluated the effects of diazepam and buspirone on SRT. SRT, related to attentional processes, is measured in two conditions: the 'gap' and the 'overlap' paradigm. In the first condition a delay between the offset of the fixation spot and the onset of a target is present, while in the second paradigm the offset of the spot is overlapped by the onset of the target. The difference between these two paradigms allowed to examine the putative drug effects on a shifting process of attention, especially the first of the three sub-processes: disengagement of attention from the current focus (a fixation point). It was hypothesised that diazepam with its hypnotic and sedative actions might affect selectively this process since the latter process demands more control than the two other more automatic sub-processes of the shifting process of attention: shifting to a new target point or the reengagement of attention in this location. In that case diazepam might specifically enhance SRTs in the overlap condition. It was also hypothesised that the effects of buspirone might be smaller, due to a lack of hypnotic and sedative actions. It was found that diazepam prolonged SRTs, reduced the number of fast saccades, and increased the number of slow saccades. The effects were identical

for the two conditions. This was not in the agreement to what was expected. Since the gap and the overlap paradigm differ only in whether or not a disengagement occurs, it can be concluded that the disengagement process is not disrupted by the drug. Therefore, the prolonged SRTs after diazepam are caused by one or both remaining processes of the attention shifting process. Buspirone had no significant effects on SRT. Therefore, it is possible that the vigilance-lowering properties of diazepam slowed down the shift or the reengagement of attention and that this is the cause of the prolonged latencies of SRT.

Both tonic and phasic heart beat might indicate vigilance. The experiment described in **Chapter 3** examined the influence of diazepam and buspirone on tonic heart rate (HR) and on the decelaratory (ECR1) and the acceleratory (ECR2) component of the evoked cardiac response (ECR). This was done in a stimulus evaluation task. The effects of drugs on HR as well as on ECR1 and ECR2 were related to two aspects of stimulus significance: attention and signal value. Attention is associated with prestimulus vigilance and may also have preparatory effects apparent in shifts in HR. The signal value of a stimulus is considered as an index of cognitive load. The significance of the stimulus was manipulated by an instruction: count the successive stimuli. In the control condition the same stimuli were given but there was no instruction. It was hypothesised that diazepam and buspirone would differentially modulate both prestimulus HR and poststimulus aspects of cardiac activity in the context of variation in stimulus significance. Because of the sedative effects of diazepam it was expected that this drug would reduce vigilance expressed in an increased prestimulus HR levels and in the reduced ECR1, compared to buspirone. Next, if the sedative effects also interfere with effortful cognitive processing, ECR2 is expected to be reduced by diazepam. As hypothesised, it was found that diazepam increased HR relative to placebo, in contrast to buspirone, which produced a decrease in HR. These drug-induced prestimulus HR level effects were associated with a differential deceleration in ECR1. The drug effect on ECR1 appeared to reflect differences in prestimulus vigilance, additionally evaluated subjectively with the Subjective Alertness Scale (SAS). Opposite effects of the drugs were also observed in acceleration of ECR2. These effects were independent from the prestimulus drug effects. Compared with placebo, buspirone appeared to enhance the acceleratory component in the count condition, while diazepam led to an apparent reduction of this component. The decrease in ECR2 after diazepam indicates reduction in attentional engagement of the subject in the task. This can lead towards a reduced cognitive-motivational processing of the stimulus. Enhancement of ECR2 after buspirone reflects an increase in cognitive effort and engagement in the task.

The experiment presented in **Chapter 4** questioned the effects of diazepam and buspirone on P300 and subsequent late positivity in event related potentials (ERPs). This was done in order to investigate the differential effects of diazepam and buspirone on cognitive

processes expressed in components of ERPs. At first, the changes of vigilance and attention prompted by the subject's involvement in the oddball task were assessed. This aim was achieved by comparing ERPs produced by the same physical stimulus (the standard stimulus of an oddball task), presented under two different (neutral and oddball) conditions. Secondly, the influence of diazepam on cognitive processing of task relevant stimuli was investigated. For this purpose, the second, classical, comparison between ERPs produced by the standard and the target stimuli of the oddball task was performed. The data of the first comparison and the results of the subjective evaluation of the level of vigilance indicate that the long-lasting and tiring task increased fatigue in all groups as measured with the SAS but this had no effects on the involvement in the oddball tasks in the buspirone and the placebo group. The data of the second comparison, combined with a separate analysis of an amplitude of P300, suggested that cognitive processing of relevant stimuli is reduced after diazepam. This impairment is also reflected in a poorer overt performance in the oddball task. In contrast to diazepam, buspirone did not appear to influence ERPs or overt performance. Therefore, the effects of diazepam might be associated with the sedative effects leading towards reduced level of vigilance.

The drug effects were measured in two post-stimulus windows. The windows reflected respectively the P300 component of the ERPs and the late slow wave positivity. There were no drug effects in the second window. The lack of drug effects in this window was surprising, considering the reported inverse relationship between late slow wave positivity and accuracy. Next, the placebo data suggest that late slow positivity was most clearly revealed from the first comparison. There was relatively small positivity in the second comparison. It was thought that the difference between the target and standard stimuli might have been too large and thus the difficulty level too small, in order to obtain significant amounts of positivity in the second window. Therefore, late slow wave positivity was more closely investigated in a drug-free experiment described in **Chapter 5**. The purpose of this experiment was to investigate the relationship between various types of slow wave positivity. Two parameters were manipulated: the level of difficulty of the oddball task and the requirement to make a motor response. Based on the previous experiment and on the literature, it was hypothesised that the motor response will influence positivity of the P300 and that the level of difficulty will be expressed in the second window. Again, two comparisons between ERPs were made. The first one was between standard and target stimuli in an easy and difficult oddball task with and without required motor responses. The second comparison was between ERPs evoked by the same stimuli, once presented as target in the oddball tasks and once in a neutral condition. The data from the first comparison show that positivity in the first window was sensitive for the motor response and in the second window for the level of difficulty in the first comparison. In the second comparison the level of difficulty was without effects, whereas the execution of a motor response yielded

more positivity in the first window. These findings underline the conclusion that different types of late positivity are directly related to specific kinds of cognitive activity (including pre-motor) and that different task manipulations can influence various types of positivity in event related potentials.

The experiment described in **Chapter 6** investigated the effects of diazepam and buspirone on cognitive processes, especially, on memory processes. The purpose of this experiment was to investigate whether buspirone might also induce anterograde amnesia and retrograde facilitation, which is found after diazepam. Next, it was questioned whether differences in side-effects between buspirone and diazepam, especially regarding vigilance, can be held responsible for putative differences on cognition. Finally, it was enquired whether the effects of anxiolytic drugs on cognition are related to their anxiolytic actions. The evaluation of the effects of both drugs was done with a neuropsychological test battery, including memory tests and a subjective evaluation of the level of vigilance. Tests were exposed twice: before and after intake of drug or placebo. Next to this, an evaluation session took place one week later. All significant differences between groups were found in the post-drug part and in the evaluation session, not prior to drug intake. Diazepam exerted major effects on memory, impaired performance of attention and concentration, as well as psychomotor tests. Next, diazepam decreased alertness. In particular, long term memory had deteriorated, which was interpreted as anterograde amnesia. One week later, more items were recalled from the pre-drug session compared to the number of items from the post-drug session. This was interpreted as retrograde facilitation. Buspirone did not induce changes in vigilance and had no effects on performance of tests in the post-drug experimental session. One week later, a small memory decrement was noticed for verbal items. This could be considered as a sign of anterograde amnesia but the disruptive effects of diazepam outweigh the small effects of buspirone. Buspirone did not induce retrograde facilitation. Overall, it was concluded that the effects of diazepam on cognition might be mediated by its decreasing effects on vigilance as measured with SAS. It was further concluded that cognitive effects are not related to the anxiolytic properties of the drug.

Therefore, the next experiment described in **Chapter 7** was performed in order to evaluate further a relation between vigilance and memory after diazepam. The diazepam-induced effects on memory were compared with methylphenidate (a stimulant drug, thought to increase vigilance). It was questioned whether opposite effects of diazepam and methylphenidate can be observed with respect to vigilance and memory. Next, the experiment aimed to describe in terms of the Atkinson and Shiffrin theory the effects of memory induced by both drugs. More specifically, it was examined whether both drugs affect similarly the immediate and delayed recall in a free memory test and whether a primacy and recency effect are equally sensitive for the drugs. It was found that diazepam reduced and methylphenidate increased level of vigilance as

measured with a subjective alertness scale. Anterograde amnesia was found after diazepam. Although a correlation between alertness and memory was found after methylphenidate, there was no anterograde facilitation. However, it could not be excluded that a ceiling effect, facilitated by the design of the experiment, was responsible for the lack of memory improvement after methylphenidate. This ceiling effect in the recall of this test was successfully prevented in an additional experiment. Again, no effects on memory were found although methylphenidate induced subjective changes in alertness. In all, it seems clear that diazepam influences memory processes. More specifically the primacy effect during immediate recall but not the recency effect was impaired after diazepam. On the contrary, primacy and recency effects were affected after diazepam in the delayed recall of 15 words. Although vigilance might play a role in a recall in memory test, the amnestic effects of diazepam seems to be due to impaired processes of memorising: rehearsals providing transfer of information from short (STM) to long term memory (LTM), coding processes in STM and consolidation in LTM than just to a non-specific lowering of vigilance.

In the last chapter - **Chapter 8** - the results of the experiments of the preceding chapters are discussed. In separate paragraphs of Chapter 8, the effects of diazepam on particular variables are analysed in terms of cognitive processes. Possible relations between variables such as SRT and the amplitude of P300 are discussed. The effects of diazepam on event related potentials (ERPs) are discussed in the scope of the additional drug-free ERP experiment. Further, the effects of diazepam on memory are discussed in terms of the Atkinson and Shiffrin model of memory. This model is also described in Chapter 8. Next, the relation between the amnestic effects of diazepam and the level of vigilance is analysed. The effects of buspirone on all variables are summarised in a separate paragraph. Buspirone lacks the cognitive deficits found after diazepam. Interestingly, evidence was found that buspirone might have certain stimulatory effects. The discussion leads towards three general conclusions. At first, it is concluded that the diazepam-induced level of vigilance does not play an important role in the amnestic properties of the drug. Secondly, the amnestic effects of diazepam are related to impaired processes of memorising. It is suggested that the rehearsal of information providing transfer of information from STM to LTM is impaired by diazepam. Next, the coding processes involved in rehearsals as well as consolidation in LTM might be also affected by the drug. Thirdly, attentional processes as revealed by the various psychophysiological variables and neuropsychological attention tasks, were disrupted after diazepam administration. It is suggested that these attentional changes can influence the performance of the recall scores. It also seems that slowing down of attentional processes might reduce the quantity as well as the speed of rehearsals. Finally, suggestions for further research on cognitive effects of diazepam intake are given. Proposed experiments deal with further analysis of effects of diazepam on memory and ERPs as well as

with an evaluation of possibilities to prevent amnestic effects of the drug.

Het centrale thema van dit proefschrift is de vraag of de kalmerende en sedatieve eigenschappen van diazepam die leiden tot een afname van attentie en vigilantie, tevens verantwoordelijk zijn voor een verminderd functioneren van het geheugen. Voorts is er de vraag of dit verminderd functioneren van het geheugen gerelateerd is aan verstoringen van andere aspecten van de verwerking van informatie. De effecten van diazepam (Valium®) (een klassiek sederend anxiolytium uit de benzodiazepine familie) werden vergeleken met de effecten van buspirone (Buspar®) (een nieuwer anxiolyticum zonder sedatieve eigenschappen). Dit werd gedaan om vast te stellen of de effecten van diazepam op het geheugen gerelateerd zijn aan de afname van vigilantie, danwel aan de anxiolytische werking ervan. Daaropvolgend werden de effecten van diazepam vergeleken met die van methylphenidate (Ritalin®) (een stimulantium van het amfetamine type), teneinde het verband tussen vigilantie en geheugen op tegengestelde wijze te onderzoeken. Geheugen en aandacht worden beschouwd al processen die onderling afhankelijk zijn. Om de amnestische werking van diazepam te evalueren, werden zowel geheugen- als aandachtsprocessen onderzocht.

Hoofdstuk 1 introduceert het begrip 'vigilantie' en beschrijft methoden om een dergelijk fenomeen te meten. Vervolgens worden in dit hoofdstuk tests geïntroduceerd voor het meten van 'performance' (geheugen, aandacht, concentratie en tevens motorische variabelen, 'subjective states', én fysiologische grootheden zoals 'saccadische reactietijd' (SRT), 'hartslag' (HR), 'evoked cardiac responses' (ECR) en 'event related potentials' (ERP). Alle fysiologische variabelen worden gekarakteriseerd binnen de kaders van paradigma's waarin ze gemeten worden. Verder worden de relaties van deze parameters met cognitieve processen besproken. Tevens worden de gebruikte psychoactieve stoffen beschreven met betrekking tot hun werking en hun mogelijke bijwerkingen.

Het experiment beschreven in **Hoofdstuk 2** evalueert de effecten van diazepam en buspirone op SRT. Deze reactietijd die gerelateerd is aan attentionele processen, werd gemeten in twee condities: in de 'gap' en de 'overlap' conditie. In de eerste conditie verscheen de target nadat het fixatiepunt was verdwenen, terwijl in de tweede conditie de target al verschijnt wanneer het fixatiepunt nog zichtbaar is. Het verschil tussen deze twee condities stelt ons in staat om het vermeende effect van medicatie te onderzoeken op aandachtsveranderingen ('shifting process in attention'), met name de eerste van drie te onderscheiden subprocessen: het ontbinden ('disengagement') van de aandacht van het fixatiepunt. De hypothese was dat diazepam met zijn hypnotische en sedatieve eigenschappen, het voornoemde proces selectief zou beïnvloeden omdat dit proces meer

sturing behoeft dan de twee andere, meer automatische subprocessen binnen het proces van aandachtsverandering: het verplaatsen van de aandacht naar een nieuwe targetpositie en het weer verbinden van de aandacht aan deze nieuwe locatie. In dat geval zou met name diazepam de SRTs in de 'overlap' conditie doen toenemen. Een andere hypothese was dat de effecten van buspirone kleiner zouden zijn omdat er geen sprake is van hypnotische en sedatieve werking. Gevonden is dat diazepam de SRTs verlengt, en zorgt voor een afname van het aantal snelle saccades tegelijkertijd met een toename van het aantal langzame saccades. De effecten waren identiek voor beide condities. Dit kwam niet overeen met wat werd verwacht. Omdat de 'gap' en 'overlap' conditie slechts verschillen met betrekking tot het ontbinden van de aandacht, kan worden geconcludeerd dat dit proces niet wordt verstoord door het medicament. Daarbij werden de verlengde SRTs na diazepam veroorzaakt door een effect op één of beide van de overgebleven subprocessen binnen de aandachtsverandering. Buspirone had geen significant effect op SRT. Daarom is het mogelijk dat de vigilantieverlagende eigenschappen van diazepam de verplaatsing of het weer verbinden van de aandacht heeft vertraagd. Dit zou de oorzaak van de langere SRTs zijn.

Zowel tonische als fasische hartslagveranderingen kunnen een indicatie van vigilantie zijn. In het in **Hoofdstuk 3** beschreven experiment werd de invloed van diazepam en buspirone op de tonische hartslag (HR) onderzocht, alswel op de fasische hartslag ('evoked cardiac response' - ECR). Op deze response wordt een decelererende (ECR1) en een accelererende (ECR2) component onderscheiden. In het experiment werd een 'stimulus evaluatie taak' gebruikt. De effecten van de medicatie op de hartslag alswel op ECR1 en ECR2 werden gerelateerd aan twee aspecten van de stimulus waarde: aan aandacht en aan de signaalwaarde. Aandacht, geassocieerd met prestimulus vigilantie, kan vastgesteld worden aan de hand van HR. De signaalwaarde van een stimulus wordt beschouwd als een index voor cognitieve belasting. De significantie van de stimulus werd gemanipuleerd met behulp van een instructie om stimuli te tellen; in een controlegroep werden dezelfde stimuli gepresenteerd zonder instructie. De hypothese was dat diazepam en buspirone zowel de prestimulus HR als de poststimulus aspecten van de cardiale activiteit in een context van variatie van stimulus-significantie op verschillende wijze zouden moduleren. Vanwege de sedatieve effecten van diazepam werd verwacht dat deze stof de vigilantie zou doen afnemen, hetgeen tot uitdrukking zou komen in een toegenomen prestimulus HR niveau en in een gereduceerde ECR1. Dit zou niet het geval zijn bij het niet-sedatieve buspirone. Indien de sedatieve effecten van diazepam ook zouden interfereren met intensieve cognitieve verwerking, werd een reductie door diazepam van ECR2 verwacht. Overeenkomstig de voorspelling werd gevonden dat diazepam de HR

deed toenemen ten opzichte van een placebo. Dit in tegenstelling tot buspirone dat een afname in HR bewerkstelligde. De door medicatie veroorzaakte differentiële prestimulus HR niveau effecten bleken geassocieerd met een verschil in deceleratie in ECR1. Het drugeffect op ECR1 leek de verschillen in prestimulus vigilantie weer te geven. Dit werd aanvullend subjectief geëvalueerd met de 'Subjective Alertness Scale' (SAS). De tegenovergestelde effecten van de medicijnen werden ook waargenomen in acceleratie van de ECR2. Deze effecten waren onafhankelijk van de drug geïnduceerde prestimulus effecten. Vergeleken met een placebo leek buspirone de acceleratoire component in de tel-conditie te versterken, terwijl diazepam leidde tot een klaarblijkelijke afname van deze component. De afname in ECR2 na diazepam wijst op een verminderde inzet van aandacht of op een afgenomen cognitief-motivationele verwerking van de stimulus. De versterking van ECR2 na buspirone dient op dezelfde wijze te geschieden, maar dan tegenovergesteld.

In het in **Hoofdstuk 4** gepresenteerde experiment werden de effecten van diazepam en buspirone op P300 en daaropvolgend vertraagde positiviteit ('late positivity') in 'event related potentials' (ERPs) onderzocht. Het doel was om de differentiële effecten van diazepam en buspirone op cognitieve processen uitgedrukt in componenten van ERPs te onderzoeken. Ten eerste werden de veranderingen van vigilantie en aandacht ten gevolge van de betrokkenheid van de proefpersoon by de 'oddball' taak vastgesteld. Dit werd bereikt door de ERPs van identieke stimuli onder twee verschillende omstandigheden te vergelijken: als neutrale stimulus en als standaard stimulus in de 'oddball' taak. Ten tweede werd de invloed van diazepam op de cognitieve verwerking van taak-gerelateerde stimuli onderzocht. Hiervoor werd de tweede (klassieke) vergelijking uitgevoerd tussen ERPs geproduceerd met de standaard- en de target stimuli van de oddball taak. De data van de eerste vergelijking en de resultaten van de subjectieve evaluatie van het vigilantieniveau wijzen uit dat de langdurige en vermoeiende taak de vermoeidheid in alle groepen deed toenemen. Echter, dit had geen effect op de betrokkenheid die gezien werd in de oddball taak in de buspirone en de placebo groep. De data van de tweede vergelijking, gecombineerd met een aparte analyse van een amplitude van P300, wezen erop dat de cognitieve verwerking van relevante stimuli was gereduceerd na diazepam. Deze teruggang bleek ook uit de verminderde overte prestaties in de oddball taak. In tegenstelling tot diazepam, leek buspirone geen invloed te hebben op ERPs of overte prestaties. Daarom hadden de effecten van diazepam mogelijk te maken met de sedatieve werking die leidde tot een gereduceerde vigilantie. Het effect van medicatie werd gemeten in twee post-stimulus vensters van de ERP. Deze vensters gaven respectievelijk de P300 component van de ERPs en de 'late slow wave' positiviteit weer. Er waren geen effecten van medicatie in het tweede venster. Het ontbreken van een drug effect was een verrassing, gezien het gerapporteerde

inverse verband tussen 'late slow wave' positiviteit en accuratesse. Vervolgens suggereren de placebo data dat de 'late slow wave' positiviteit het beste zichtbaar is in de eerste vergelijking. De afwezigheid van veel positiviteit in de tweede vergelijking kon veroorzaakt zijn door het feit dat de afstand tussen target- en standaard stimuli te groot was. Zodoende was de moeilijkheidsgraad te laag teneinde significante hoeveelheden positiviteit in het tweede venster te krijgen.

Daarom werd 'late slow wave' positiviteit nader onderzocht in een niet-medicamenteus experiment en dit is beschreven in **Hoofdstuk 5**. Het doel van dit experiment was de relaties tussen verschillende typen 'late slow wave' positiviteit te onderzoeken. Twee parameters werden gemanipuleerd: de moeilijkheidsgraad van de oddball taak en de vereiste om een motorische respons te produceren. Gebaseerd op het vorige experiment en de literatuur werd de hypothese opgesteld dat de motorische respons de positiviteit van de P300 zou beïnvloeden en dat de moeilijkheidsgraad tot uitdrukking zou komen in de positiviteit van het tweede venster. Wederom werden twee vergelijkingen tussen ERPs gemaakt. De eerste was tussen standaard- en target stimuli van de eenvoudige en moeilijke oddball taak, met of zonder vereiste om een motorische respons uit te voeren. De tweede vergelijking was tussen ERPs geproduceerd door dezelfde stimuli, de ene keer gepresenteerd als targets in de oddball taak en de andere keer in een neutrale conditie. De resultaten van de eerste vergelijking toonden aan dat de positiviteit in het eerste venster gevoelig was voor de motorische respons, terwijl de moeilijkheidsgraad in het tweede venster tot uiting kwam. In de tweede vergelijking bleef de moeilijkheidsgraad manipulatie zonder effect, terwijl het uitvoeren van een motorische respons meer positiviteit opleverde in het eerste venster. Deze resultaten onderstrepen de conclusie dat verschillende typen van late positiviteit direct gerelateerd zijn aan specifieke soorten cognitieve activiteit (inclusief pre-motorische responsen) en dat verschillende taakmanipulaties de diverse soorten positiviteit in ERPs kunnen beïnvloeden.

Het experiment beschreven in **Hoofdstuk 6** onderzocht het effect van diazepam en buspirone op cognitieve processen, met name op geheugenprocessen. Het doel van dit experiment was te onderzoeken of buspirone eveneens anterograde amnesie en retrograde facilitatie kan veroorzaken zoals gevonden na diazepam. Vervolgens werd de vraag gesteld of verschillen in bijwerkingen tussen buspirone en diazepam, voornamelijk met betrekking tot vigilantie, verantwoordelijk zouden kunnen zijn voor de verschillende invloed op cognitieve functies. Als laatste werd onderzocht of de effecten van deze anxiolitische medicijnen op cognitie gerelateerd zouden kunnen zijn aan hun anxiolitische werking. De effecten van beide medicijnen werden geëvalueerd met een neuropsychologische testbatterij, welke een geheugentest en een subjectieve evaluatie van het vigilantieniveau

bevatte. De testen werden tweemaal uitgevoerd: voor en na het toedienen van het medicijn of de placebo. Tevens vond een week later een evaluatie-sessie plaats. Alle significante verschillen tussen groepen werden gevonden in de na-test en in de evaluatie-sessie, en niet voorafgaand aan de toediening van het medicijn. Diazepam had een grote invloed op het geheugen. Het veroorzaakte tevens een afname van aandacht, van concentratie alsmede van prestaties op een psychomotorische test. Tenslotte reduceerde diazepam de alertheid. Met name het lange termijn geheugen werd aangetast, hetgeen geïnterpreteerd werd als anterograde amnesie. Een week later werden meer items herinnerd van de voor-test sessie dan van de na-test sessie. Dit werd geïnterpreteerd als retrograde facilitatie. Buspirone veroorzaakte geen verandering van vigilantie en had geen effect op de prestaties tijdens de na-test sessie. Een week later werd een kleine geheugenafname geconstateerd voor verbale items. Dit kan gezien worden als een teken van anterograde amnesie, maar bij het grote effect van diazepam valt het geringe effect van buspirone in het niet. Verder veroorzaakte buspirone geen retrograde facilitatie. In het algemeen kan geconcludeerd worden dat de effecten van diazepam op cognitie kunnen zijn voortgekomen uit de afname van vigilantie, zoals die ook gemeten kan worden met een subjective alertness scale. Voorts werd weer vastgesteld dat de cognitieve effecten niet zijn gerelateerd aan de anxiolytische eigenschappen van het medicijn.

Om de relatie tussen vigilantie en geheugen na diazepam verder te onderzoeken, werd een volgend experiment, beschreven in **Hoofdstuk 7**, uitgevoerd. Het door diazepam veroorzaakte effect op geheugen werd vergeleken met methylphenidate (een stimulerend medicijn, waarvan wordt verondersteld dat het vigilantie doet toenemen). De vraag werd gesteld of tegengestelde effecten van diazepam en methylphenidate kunnen worden waargenomen met betrekking tot vigilantie en geheugen. Vervolgens werd gepoogd om met behulp van de theorie van Atkinson en Shiffrin de door beide medicijnen veroorzaakte effecten op het geheugen te beschrijven. Meer specifiek werd gekeken of beide medicijnen op overeenkomstige wijze de onmiddellijke en verlate herinnering ('immediate and delayed recall'), in een vrije geheugentest aanttasten, en voorts of 'primacy' en 'recency' effecten in gelijke mate gevoelig waren voor beide stoffen. Er werd gevonden dat het vigilantieniveau, zoals gemeten met een 'subjective alertness scale' (Thayer), afnam met diazepam en toenam met methylphenidate. Na diazepam werd anterograde amnesie gevonden. Hoewel een correlatie tussen alertheid en geheugen werd gevonden na methylphenidate, kon er geen anterograde facilitatie worden vastgesteld. Het kan echter niet worden uitgesloten dat het ontbreken van een geheugenverbetering na methylphenidate het gevolg was van een plafondeffect, voortkomend uit het experimentele design. Een dergelijk plafondeffect in geheugen werd voorkomen in een additioneel

experiment. Wederom werden er geen geheugeneffecten gevonden, hoewel methylphenidate subjectieve veranderingen in alertheid veroorzaakte. Al met al is het wel duidelijk dat geheugenprocessen worden beïnvloed door diazepam. Meer specifiek was het 'primacy' effect tijdens 'immediate recall verminderd na diazepam. Hieraan tegengesteld waren het 'primacy' en 'recency' effect aangetast door diazepam in een 'delayed recall' van 15 woorden. Hoewel vigilantie betrokken kan zijn bij recall in een geheugentest, leken de amnestische effecten van diazepam minder het gevolg te zijn van enkel een niet-specifieke verlaging van vigilantie dan wel van een vermindert proces van memoriseren. Het leek erop dat diazepam de transfer van 'short term memory' (STM) naar 'long term memory' (LTM) door herhalingen, door coderingsprocessen in STM en door consolidatie in LTM, aantast.

In het laatste hoofdstuk (**Hoofdstuk 8**) worden de resultaten van de voorgaande hoofdstukken besproken. In verschillende hoofdstukken worden de effecten van diazepam op bepaalde variabelen geanalyseerd in termen van cognitieve processen. Mogelijke relaties tussen variabelen, zoals SRT en de amplitude van P300, worden aangegeven. De effecten van diazepam op ERPs worden besproken vanuit het gezichtspunt van het toegevoegde niet-medicamenteuze ERP experiment. Verder worden de effecten van diazepam op het geheugen besproken in termen van het geheugen model van Atkinson en Shiffrin. Dit model is beschreven in Hoofdstuk 8. Vervolgens wordt het verband tussen de amnestische effecten van diazepam en het vigilantieniveau geanalyseerd. De effecten van buspirone op alle variabelen worden samengevat in een aparte paragraaf. Het lijkt erop dat buspirone geen effect heeft op cognitieve processen in vergelijking met een placebo maar wellicht wel ten opzichte van diazepam. Interessant is dat er aanwijzingen zijn gevonden dat buspirone bepaalde stimulerende effecten kan hebben. De discussie leidt tot drie algemene conclusies. Ten eerste is er vastgesteld dat het door diazepam veroorzaakte vigilantie niveau geen belangrijke rol speelt bij de amnestische eigenschappen van het medicament. Ten tweede zijn de amnestische effecten van diazepam gerelateerd aan de aantasting van memoriseringsprocessen. Er wordt aangegeven dat de herhaling ('rehearsal') van informatie die nodig is voor de overdracht van informatie van STM naar LTM wordt aangetast door diazepam. Ook wordt aangegeven dat coderingsprocessen die betrokken zijn bij dit herhalen, alsmede consolidatie in LTM, kunnen zijn aangedaan door het medicament. Ten derde blijken aandachtsprocessen verstoord na toediening van diazepam. Dit is duidelijk geworden bij meting van de verschillende psychofysiologische variabelen en de neuropsychologische aandachtstaken. Alles wijst erop dat deze veranderingen in aandacht van invloed geweest kunnen zijn op de prestaties van de 'recall' scores. Tevens zijn er aanwijzingen dat de vertraging van de aandachtsprocessen zowel de hoeveelheid als de snelheid van de 'rehearsals' kan terugbrengen.

Tenslotte worden suggesties gedaan voor verder onderzoek naar de cognitieve effecten van diazepam. De voorgestelde experimenten hebben betrekking op verdergaande analyses van de effecten van diazepam op geheugen en ERPs, alsmede een evaluatie van mogelijkheden om de amnestische effecten van het medicament te ondervangen.

SUMMARY IN POLISH (STRESZCZENIE)

Głównym celem pracy było stwierdzenie czy sedatywne właściwości diazepamu (Relanium®), obniżające poziom aktywacji są odpowiedzialne za zaburzenia pamięci oraz czy obniżenie procesów pamięciowych związane jest z innymi zaburzeniami procesów poznawczych pod wpływem diazepamu. W tym celu porównywany był wpływ diazepamu z buspironem (Spamilan®). Buspiron jest lekiem przeciwlękowym, który nie posiada sedatywnych właściwości. Porównanie to miało wykazać, czy wpływ diazepamu na procesy poznawcze jest związany z obniżoną aktywacją, czy raczej jest związany z jego przeciwlękowym działaniem. Wpływ diazepamu był również porównywany z methylphenidate (Ritalin®) (lekiem pobudzającym) w celu dalszej analizy związku pomiędzy aktywacją i zaburzeniami pamięci.

Pamięć i uwaga uznawane są za procesy wzajemnie się uzupełniające. Dlatego też, w celu analizy zaburzeń pamięci wywołanych przez diazepam, badano nie tylko pamięć ale również procesy uwagi.

Rozdział 1 (Wstęp) charakteryzuje aktywację i metody jej pomiaru. Ponadto w rozdziale tym przedstawione są testy badające pamięć, uwagę połączoną z koncentracją, motorykę jak również testy pozwalające na subiektywną ocenę aktywacji. Następnie opisano w nim zmienne fizjologiczne zastosowane w eksperymentalnej części pracy, takie jak: sakadyczny czas reakcji 'saccadic reaction time' (SRT), rytm bicia serca 'heart rate' (HR), odpowiedzi wywołane serca 'evoked cardiac response' (ECR) i potencjały zdarzeniowe 'event related potentials' (ERPs) oraz ich związki z procesami poznawczymi. W dalszej części rozdziału scharakteryzowano zastosowane leki, ich działanie i skutki uboczne.

Celem eksperymentu opisanego w **Rozdziale 2** było zbadanie wpływu diazepamu i buspironu na SRT, który związany jest z z procesami uwagi. SRT mierzony był w dwóch warunkach badawczych: w 'gap'[9] i 'overlap' paradygmacie. 'Gap' paradygmat charakteryzuje się przerwą wystepującą pomiędzy momentem zniknięcia punktu fiksacji a pojawieniem się bodźca. Natomiast w 'overlap' paradygmacie punkt fiksacji zanika w czasie pojawienia sie bodźca. Różnica ta pozwala zbadać wpływ leku na proces przenoszenia uwagi 'shifting process of attention' a w szczególności na jeden z trzech jego podprocesów: na odangażowanie uwagi z punktu fiksacji 'disengagement of attention from the current focus - a fixation point'. Założeniem badawczym eksperymentu było stwierdzenie, czy diazepam, z jego usypiającymi i sedatywnymi właściwościami może wpływać wybiórczo na proces odangażowywania uwagi. Proces ten jest bardziej kontrolowany przez osobę badaną niż dwa pozostałe podprocesy, które wydają się być

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[9] W celu uniknięcia tworzenia neologizmów, w niektórych przypadkach została zachowana angielskojęzyczna terminologia naukowa.

zautomatyzowane: przenoszenie uwagi na bodziec 'shifting of attention to a saccade stimulus' i angażowanie uwagi na bodźcu 'reengagement of attention in location of the target'. W eksperymencie zakładano również, że wpływ diazepamu może być szczególnie wyraźny w 'overlap' paradygmacie. Następnym założeniem badawczym było stwierdzenie, że wpływ buspironu będzie mniejszy na skutek braku usypiających i sedatywnych właściwości. Dane experymentalne wskazują, iż diazepam wydłużył SRTs, zmniejszył ilość szybkich sakad 'saccades' zwiększając jednocześnie ilość wolnych sakad. Efekt ten był identyczny w 'gap' i 'overlap' paradygmacie. Wynik ten był sprzeczny z oczekiwanym. W związku z tym, iż w 'gap' paradygmacie występuje proces odangażowania uwagi a w 'overlap' paradygmacie nie ma go, można wyciągnąć wniosek, że diazepam nie wpływa na proces odangażowania uwagi z punktu fiksacji. Dlatego też, wydaje się, iż wydłużony na skutek działania diazepamu SRT związany jest z wybiórczym wpływem leku na proces przenoszenia uwagi na bodziec lub na proces angażowania uwagi na bodźcu, albo też na obydwa procesy jednocześnie. Buspiron nie wywołał żadnych zmian w SRT. Dlatego można wnioskować, że obniżona aktywacja wywołana diazepamem powoduje wydłużenie SRT.

Toniczna i fazowa miara pracy serca wykazuje zmiany w aktywacji. Eksperyment opisany w **Rozdziale 3** bada wpływ diazepamu i buspironu na toniczny HR i na deceleracyjny (ECR1) i akceleracyjny (ECR2) komponent ECR, mierzony w zadaniu oceniającym bodźce. Wpływ leku na HR jak również na ECR1 i ECR2 był oceniany w aspekcie 'uwagi skierowanej na bodziec' i 'znaczenia bodźca'. 'Uwaga skierowana na bodziec' związana jest z przedbodźcową aktywacją i z oczekiwaniem na bodziec, co prowadzi do zmian w HR. 'Znaczenie bodźca' uznawane jest za wyznacznik 'cognitive load'. Znaczenie bodźca modulowano poprzez instrukcję 'licz bodźce'. W zadaniu kontrolnym nie podawano instrukcji. Hipotezą badawczą było pytanie: czy obydwa leki różnią się pod względem ich wpływu na aktywność serca mierzoną przed i po wyzwoleniu bodźca w kontekście zmian jego znaczenia? Oczekiwano, iż na skutek sedatywnego działania diazepam obniży aktywację wyrażającą się w zwiększonym poziomie HR i zredukowaną deceleracją w ECR1 w porównaniu do buspironu. Spodziewano się również, że sedatywne działanie leku będzie wpływało na poznawczą analizę bodźca, przejawiającą się poprzez redukowaniem akceleracji w ECR2. Wyniki eksperymentu wskazują, że diazepam przyśpieszył HR w porównaniu do placebo a buspiron zwolnił pracę serca. Zmiany HR wywołane przez leki wpływały na kształt ECR1. Dlatego też ECR1 odwzorował poziom aktywacji przed zadziałaniem bodźca. Poziom ten oceniany był również subiektywnie przy użyciu kwestionariusza 'Subjective Alertness Scale' (SAS). Leki wpływały przeciwnie na ECR2. Ich wpływ był niezależny od zmian w HR. W porównaniu do placebo w zadaniu z instrukcją 'licz bodźce' diazepam zmniejszył akcelerację a buspiron ja zwiększył. Zredukowany ECR2 pod wpływem diazepamu wskazuje na obniżenie zaangażowania uwagi w

sytuacji zadaniowej co może doprowadzić do poznawczo-motywacyjnego zredukowania przetwarzania bodźca. Zwiększenie ECR2 pod wpływem buspironu wskazuje na zwiększony wysiłek poznawczy i zaangażowanie w zadanie.

Eksperyment opisany w **Rodziale 4** analizuje wpływ diazepamu i buspironu na procesy poznawcze odwzorowywane w dwóch komponentach ERPs: P300 i następującym po nim 'late slow wave positivity'. W eksperymencie tym analizowano zmiany poziomu aktywacji i uwagi związane z zaangażowaniem się osoby badanej w zadanie 'oddball'. W tym celu porównywano ERPs wywołane przez identyczne bodźce (bodziec 'standard' z zadania 'oddball'), prezentowane w dwóch warunkach zadaniowych (oddball i neutralnym zadaniu) (Analiza 1). Następnie badano wpływ diazepamu na procesy poznawcze dotyczące bodźców definiowanych przez instrukcje ('target'). W tym celu analizowano ERPs wywołane przez bodziec 'standard' i 'target' w zadaniu 'oddball' (Analiza 2). Wyniki analizy 1 i dane związane z subiektywną oceną aktywacji wskazują, że długotrwałe i męczące zadanie zwiększyło poziom zmęczenia we wszystkich grupach badanych osób ale nie wpływało na zaangażowanie się badanych osób będących pod wpływem buspironu i placebo w zadanie 'oddball'. Wyniki analizy 2 połączone z oddzielnie przeprowadzoną analizą amplitudy P300 sugerują, iż poznawcza analiza definiowanych poprzez instrukcję bodźców zredukowana jest przez wpływ diazepamu. Efekt ten uwidacznia się również w gorszym wykonywaniu zadania 'oddball'. W przeciwieństwie do diazepamu buspiron nie miał wpływu na wykonanie tego zadania. Dlatego też wpływ diazepamu na ERPs może być związany z jego sedatywnym działaniem obniżającym poziom aktywacji.

Wpływ leku na ERPs analizowano w dwóch przedziałach czasowych mierzonych po wyzwoleniu bodźca. Pierwszy odwzorowywał P300 a drugi 'late slow wave positivity'. Leki nie wywołały żadnych zmian w przebiegu ERPs w drugim przedziale czasowym. Biorąc pod uwagę iż istnieje odwrotny związek pomiędzy 'late slow wave positivity' a precyzją wykonywania zadania, było to niezgodne z oczekiwaniami. Poza tym, wyniki z grupy placebo wskazują na występowanie 'late slow wave positivity' w analizie 1. Dlatego też przypuszcza się, że brak zmian w przebiegu 'late slow wave positivity' spowodowany był dużą różnicą pomiędzy obydwoma rodzajami bodźców w 'oddball' zadaniu. Różnica ta zredukowała tym samym poziom trudności zadania. Z tego powodu komponent 'late slow wave positivity' był ponownie analizowany w drugim ERPs eksperymencie przeprowadzanym tym razem bez użycia leku **(Rozdział 5)**. Celem tego eksperymentu była analiza związku pomiedzy różnymi typami 'slow wave positivity', w sytuacji kiedy poziom trudności zadania 'oddball' i motoryczna reakcja na zdefiniowany bodziec była manipulowana. W oparciu o eksperyment opisany w rodziale 4 i dostępną literaturę, zakładano iż motoryczna reakcja na bodziec będzie wpływała na komponent P300 ERP a poziom trudności zadania będzie determinował przebieg ERP w drugim przedziale czasowym. Podobnie jak w eksperymencie opisanym w rozdziale 4, przeprowadzane były dwie

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analizy ERPs. Pierwsza analiza przeprowadzona była pomiedzy wywołanymi przez dwa rodzaje bodźców 'standard' i 'target' ERPs. Bodźce te prezentowane były w 'łatwym' i 'trudnym' zadaniu 'oddball', w połączeniu z koniecznością reakcji motorycznej lub jej brakiem. Druga analiza przeprowadzana była pomiędzy bodźcem 'target' prezentowanym w zadaniu 'oddball' i tym samym bodźcem prezentowanym w neutralnym zadaniu. Wyniki pierwszej analizy wykazały, że reakcja motoryczna wpływa na 'positivity' w pierwszym przedziale czasowym a poziom trudności zadania wpływa na 'positivity' w drugim przedziale czasowym. Dane z drugiej analizy wskazują, iż poziom trudności nie odgrywa roli natomiast motoryczna reakcja wpływa na 'positivity' w pierwszym przedziale czasowym. Wyniki eksperymentu wskazują, że różne procesy poznawcze są bezpośrednio związane z różnymi rodzajami 'positivity' a manipulacja sytuacją zadaniową dodatkowo wpływa na przebieg 'positivity' w ERPs

Eksperyment opisany w **Rozdziale 6** analizuje wpływ diazepamu i buspironu na procesy poznawcze a w szczególności na pamięć. Celem tego eksperymentu było zbadanie czy buspiron, podobnie jak diazepam, może rownież wywoływać 'anterograde amnesia' i 'retrograde facilitation'. Ponadto celem eksperymentu było stwierdzenie, czy różnice w skutkach ubocznych pomiędzy obydwoma lekami, w szczególności uwzględniając aktywację, mogą być odpowiedzialne za różnice w procesach poznawczych. Następnym pytaniem badawczym było stwierdzenie czy wpływ leków na procesy poznawcze jest związany z ich przeciwlękowym działaniem. Wpływ leków analizowany był przy pomocy neuropsychologicznych testów, włącznie z testami pamięciowymi i subiektywną analizą aktywacji. Testy te prezentowane były osobie badanej dwukrotnie: przed i po podaniu leku lub placebo. Trzecia, ewaluacyjna część miała miejsce po upływie tygodnia. W drugiej i trzeciej części eksperymentu znaleziono statystycznie istotne wyniki. Natomiast wyniki otrzymane przed podaniem leku nie różnicowały grup między sobą. Diazepam obniżył poziom aktywacji i wywołał znaczne zmiany w procesach pamięciowych, pogorszył wykonanie testów związanych z uwagą i koncentracją oraz wykonanie testów motorycznych. Diazepam ograniczył pamięć długotrwałą co jest interpretowane jako przejaw 'anterograde amnesia'. Podczas części ewaluacyjnej okazało się, że osoby, które tydzień wcześniej zażyły diazepam, odpamietały więcej wyuczonych przed podaniem leku informacji w porównaniu z ilością odpamiętanych informacji prezentowanych w drugiej części eksperymentu. Jest to interpretowane jako przejaw 'retrograde facilitation'. Buspiron nie wpłynął ani na poziom aktywacji u osób badanych ani na wykonywanie testów. Tydzień później niewielkie zaburzenia pamięci zaobserwowane zostały w grupie osób będących uprzednio pod wpływem buspironu. Fakt ten można rownież uznać za przejaw 'anterograde amnesia'. Jednakże efekt ten był minimalny w porównaniu z 'anterograde amnesia' wywołaną przez diazepam. Na podstawie wyników można stwierdzić, iż wpływ diazepamu na procesy poznawcze może być wywołany poprzez obniżoną aktywację a nie poprzez jego przeciwlękowe właściwości.

W celu dalszej analizy związku pomiędzy zmianami aktywacji wywołanymi przez diazepam a pamięcią, przeprowadzono eksperyment opisany w **Rozdziale 7**. Diazepam był tam porównywany z methylphenidate (lekiem pobudzającym czyli zwiększającym poziom aktywacji). Celem eksperymentu było stwierdzenie czy przeciwny efekt diazepamu i methylphenidate można obserwować nie tylko w odniesieniu do aktywacji ale również w odniesieniu do pamięci. Następnym założeniem eksperymentu było opisanie wpływu obydwu leków na procesy pamięciowe w odniesieniu do Atkinsona i Shiffrina modelu pamięci. Głównym celem eksperymentu było stwierdzenie czy obydwa leki wpływają podobnie na natychmiastowe i odroczone odtwarzanie wyuczonych informacji i, czy obydwa leki wpływają podobnie na 'primacy' i 'recency' efekt związany z odtwarzaniem informacji podanych na początku i na końcu testu. Wyniki eksperymentu wskazują, że diazepam obniżył aktywację a methylphenidate ją podwyższył. Diazepam wywołał 'anterograde amnesia'. Chociaż wyniki testów wskazują na korelację pomiędzy aktywacją a pamięcią, nie znaleziono pod wpływem methylphenidate 'anterograde facilitation'. Należy jednak wziąść pod uwagę, iż brak zwiększonego odtwarzania wyuczonych informacji pod wpływem methylphenidate mógł być spowodowany 'ceiling' efektem wywołanym schematem ekperymentu. Dodatkowy eksperyment opisany w tym rozdziale skutecznie zapobiegł pojawieniu się tego efektu. Pomimo iż methylphenidate zwiększył poziom aktywacji, również i w tym eksperymencie nie znaleziono wpływu methylphenidate na procesy pamięciowe. Diazepam wpływa na procesy pamięciowe, w szczególności na 'primacy efekt' w czasie natychmiastowego odtwarzania. Diazepam nie wpłynął na 'recency' efekt w natychmiastowym odtwarzaniu. Natomiast zredukowany efekt 'primacy' i 'recency' został znaleziony w odroczonym odtwarzaniu. Aktywacja może wpływać na odtwarzanie testów pamięciowych, jednakże amnezja wywołana diazepamem wydaje się być bardziej związana z zaburzonym procesem zapamiętywania. Wydaje się, iż amnezja jest w szczególności powodowana zaburzonym powtarzaniem prowadzącym do przemieszczenia prezentowanej informacji z pamięci krótkotrwałej (STM) do pamięci długotrwałej (LTM), z zaburzonym kodowaniem informacji w STM i konsolidacją informacji w LTM.

Ostatni rozdział - **Rozdział 8** - prezentuje dyskusję wyników części eksperymentalnej. W oddzielnych podrozdziałach analizowany jest wpływ diazepamu na poszczególne zmienne w relacji do procesów poznawczych. Ponadto, przedstawiane są możliwe związki pomiędzy zmiennymi np pomiędzy amplitudą P300 i SRT. Wpływ diazepamu na ERPs omawiany jest w połączeniu z wynikami ERPs eksperymentu, przeprowadzonego bez użycia leków. Następnie, Wpływ diazepamu na procesy pamięciowe opisany jest w odniesieniu do Atkinsona i Shiffrina modelu pamięci (model ten jest również opisany w tym rozdziale). Omawiany jest również związek pomiędzy zaburzeniami pamięci wywołanymi diazepamem a poziomem aktywacji. Ponadto w rozdziale 8 omówiony został wpływ buspironu na poszczególne zmienne. Wydaje

się, że buspiron w porównaniu z placebo nie wpływa na procesy poznawcze, może mieć nawet pewien stymulujący efekt. Dyskusja wyników prowadzi do trzech ogólnych wiosków. Po pierwsze, poziom aktywacji wywołany diazepamem nie odgrywa istotnej roli w zaburzeniach pamięci. Po drugie, amnezja związana jest z procesem zapamiętywania. Sugeruje się, iż powtarzanie informacji doprowadzające do przemieszczenia sie jej z STM do LTM jest zaburzone pod wpływem diazepamu. Następnie procesy kodujące związane z powtarzaniem informacji i konsolidacją materiału w LTM są również zaburzone przez lek. Po trzecie, uwaga, jak wykazano przez zmienne psychofizjologiczne i neuropsychologiczne testy badające uwagę, jest zaburzona. Sugeruje się, że te zmiany uwagi wpływają na zapamiętywanie informacji. Wydaje się, iż spowolnienie procesów uwagi może zredukować zarówno ilość jak i szybkość powtarzania prezentowanych informacji.

W końcowej części rozdziału 8, podano sugestje związane z dalszą analizą wpływu diazepamu na procesy poznawcze. Proponowane eksperymenty związane są z możliwością analizy wpływu diazepamu na pamięć, ERPs jak również z analizą możliwości zapobiegania zaburzeniom pamięci.

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CURRICULUM VITAE

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