THE EFFECTS OF ALCOHOL AND TEMAZEPAM UPON MISMATCH NEGATIVITY

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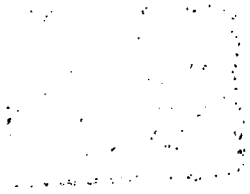

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Literature Review

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ABSTRACT

Mismatch negativity is a component of the auditory event-related potential which is elicited by stimulus change following a series of homogenous stimuli. Mismatch negativity is the subject of some debate regarding whether physical stimulus features are processed and mismatch detection conducted equally well, whether in the presence or absence of attention. Alcohol and temazepam are both drugs which have been found to attenuate other attention dependent components of the ERP. This attenuation is attributed to a reduction of attentional resources. Thus by measuring the effect of attention upon mismatch negativity under the influence of alcohol and temazepam singly, this dilemma may be resolved. If temazepam and alcohol only affect attentional components of the ERP then attenuation would only be expected in ERPs taken in conditions of attention. Furthermore if MMN is attention dependent it would be expected that these drugs administered together may produce an interactive effect upon the amplitude of mismatch negativity.

Cognitive psychophysiology is directed toward revealing the neural correlates of psychological constructs of information processing. Neural events are manifested as event-related potentials (ERPs) which are electrical recordings of neural activity which are measured from the scalp. These ERPs may be regarded as electrical indications of specific stages of information processing. Mismatch negativity (MMN) is one component of the auditory ERP. It is evoked following neural detection of a difference between a presenting stimulus and a stream of prior homogenous stimuli (Naatanen, 1988).

The automaticity of information processing is uncertain, and is thought to be affected by attention. Attention is the process by which the organism consciously perceives the environment. Perception can be preattentive and passive, or conscious and controlled, resulting in the concentration of attentional resources and processing space upon specific features of the environment (Kahneman & Treisman, 1984). Attention is known to affect the amplitude of some components of the auditory ERP because the amplitude of these components is suppressed in the absence of attention and enhanced in the presence of attention. Specifically attention is known to affect later components such as the P300 and N400 which signal information processing including stimulus encoding, evaluation, categorisation and representation in memory (Hillyard & Kutas, 1983). However, the point at which attention affects cognitive processing is a subject of controversy. One view is that attention affects only later information processing (Naatanen, 1988). The competing perspective is that attention affects both

early sensory processing and later information processing (Broadbent, 1958). Mismatch negativity is a component which may help to clarify the debate regarding the effect of attention upon sensory processing. Currently the status of MMN either as preattentive or as influenced by attention is unresolved. ERPs have been acknowledged to be related to concomitant behavioural responses as well as to the influence of chemical substances (Porjesz & Begleiter, 1993; Pietrowsky, Born, Fehm-Wolfsdorf, & Fehm, 1989). The influence of temazepam and alcohol upon MMN offer an opportunity to elucidate the relationship between MMN and attention, as alcohol and temazepam are known to reduce attentional resources (Porjesz & Begleiter, 1993; Martin, Nichols, Mills, & Siddle, 1993). Consequently, if alcohol and temazepam reduce MMN amplitude, then this will indicate that MMN is attention dependent, and therefore that sensory processing is, to some degree, dependent upon attention.

This review is directed toward investigating the role of attention in elicitation of the MMN component of the auditory event-related potential. ERPs, their nature and use as an instrument of cognitive psychophysiology will be investigated. MMN characteristics and the model comparator theory of MMN will be presented. Following this theories of attention will be presented in application to information processing, and specifically in regard to MMN. Alcohol it's nature and effect on ERPs and attention will be discussed and predictions made about the possible effects of alcohol upon MMN. Temazepam will also be analysed in regard to its effects upon attention and ERPs, and hypotheses developed about its effects

upon MMN. Subsequently, hypotheses regarding the combined effect of alcohol and temazepam upon MMN will be developed.

1. Event-related potentials

Event-related potentials (ERPs) are small electrical changes in the brain indicated by electrical activity recorded on the scalp by the electroencephalogram (EEG). By recording a large number of time locked ERPs and averaging them, unrelated activity is averaged out and a clear ERP waveform is revealed. Using this procedure a regular waveform is evoked when ERPs are repeatedly taken. Figure 1. shows a typical auditory waveform. The peaks and troughs which can be observed are labelled 'P' or 'N' dependent upon whether they reflect positive or negative electrical activity. The most well established components of the waveform are labelled 'N100', 'P200', 'N200', 'P300' according to the approximate latency at which they occur. These components have been found to be highly correlated with specific psychological constructs of cognitive events and are used to study information processing (Graham & Hackley, 1991).

Differences in the waveform can be observed and measured in response to divergent information processing conditions. The optimal way of citing these differences is by using a difference waveform. A difference waveform is calculated by subtracting an ERP recorded in the experimental condition from the ERP which is recorded in the control condition. The resultant measure indicates differences due to the independent variable. In this way ERPs can

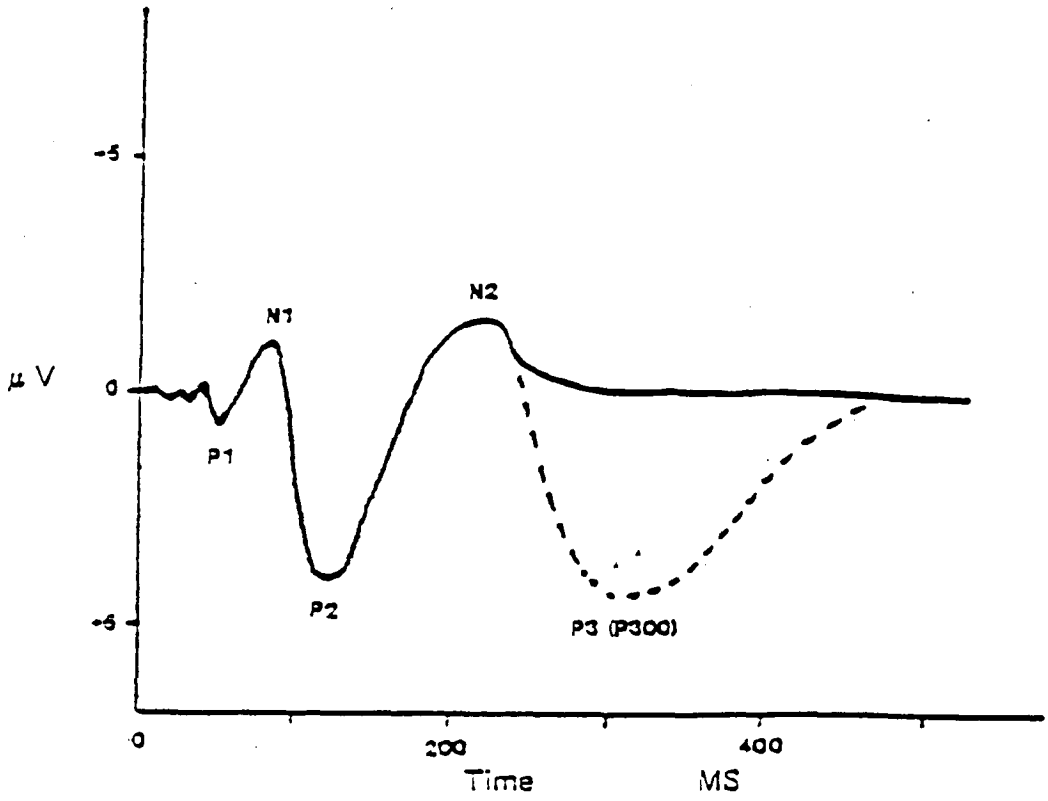

Figure 1 An event-related potential showing the significant components between 40 and 500 ms (Empson, 1986, p. 37).

be used to identify the effects of different information processing conditions.

ERPs promote understanding of the structure and organisation of information processing. Different ERP components can be related to specific stages of information processing. MMN is one component of the auditory ERP which has been attributed to detection of stimulus change.

2. Mismatch negativity

MMN is a negative component of the auditory ERP which occurs approximately 150 - 250 ms following stimulus presentation. Electrical activity which has been denoted as signifying MMN occurs primarily in the frontocentral and prefrontal right hemisphere (Paavilainen, Alho, Reinikainen, Sams, & Naatanen, 1991). The source of MMN is the supratemporal auditory cortex (Tiitinen, Alho, Huotilainen, Ilmoniemi, & Risto, 1993) which receives projections from the caudomedial geniculate nucleus of the thalamus which appears to be the initial registration of acoustic discrimination and MMN (Kraus, McGee, Littman, Nichol, & King, 1994).

MMN is not elicited in response to stimulus presentation per se, but only in response to stimulus change in a sequence of homogeneous, habituated stimuli, which has a low probability of occurring (Graham & Hackley 1991). Any physical parameter may be the medium of change or deviance, for example pitch (Naatanen 1986), intensity or duration (Naatanen, 1982), inter-stimulus interval (Ford & Hillyard, 1981; Naatanen, Jiang, Lavikainen,

Reinikainen, & Paavilainen, 1993), and abstract changes such as an unexpected variation in a pattern of stimuli (Naatanen, Schroger, Karakas, Tervaniemi, & Paavilainen, 1993; Saarinen, Paaviliainen, Schroger, Tervaniemi, & Naatanen, 1992). Repeated presentation of the deviant stimulus will result in attenuation of MMN (Cowan, Winkler, Teder, & Naatanen, 1993).

MMN is a change detection mechanism which signals environmental change to the organism (Graham & Hackley, 1991). The latency, duration, and amplitude of MMN are a function of the degree of change between the deviant presenting stimulus and the prior habituated stimuli (Winkler, Paavilainen, Alho, Reinikainen, Sams, & Naatanen, 1990). The amplitude of MMN increases according to the magnitude of stimulus deviance (Naatanen, 1988; Graham & Hackley 1991). This is consistent with the concept of MMN as having a survival function, in which greater change elicits earlier, greater MMN. However in laboratory settings MMN is generally measured when stimulus deviance is moderate as MMN is isolated from other components (N1 and P2) and observed optimally (Graham & Hackley, 1991).

MMN plays a critical survival role, in that it is the fundamental indicator of environmental change and leads to the organism becoming aware of potentially life threatening changes in the environment. It appears that MMN is a product of sensory processes, and attracts attention to changed stimuli. MMN has been recognised to play a role in attentional orienting, leading to the application of Sokolovs' (1969) model comparator theory to MMN.

3. The model comparator theory of mismatch negativity

The prevailing theory of MMN is Sokolovs' model comparator theory which Sokolov (1969) conceived to account for the orienting response (orienting response theory). Sokolov proposed the existence of cortical novelty detecting cells which contain templates of previous stimuli. These templates are a function of synaptic adaptation to static stimuli. In the static state the novelty detecting cells are inactive, however when a change occurs in the sensory information from the deviant stimulus, these cells register change and generate psychophysiological responses. Habituation to the stimulus change occurs as a result of repetition of the deviant stimulus. As the new sensory information of the deviant becomes incorporated into the neuronal model, the novelty detecting cells gradually become habituated to the change and adopt the deviant stimulus as the succeeding, static neuronal template. Once this occurs, the novelty detection cells no longer fire.

Model comparator theory was applied to MMN by Sams, Kaukoranta, Hamalainen, and Naatanen (1991) who proposed that auditory cortex feature detectors converge upon novelty detectors also contained in the auditory cortex. These auditory cortex novelty detectors contain stimulus templates which, consistent with Sokolov's model, are a function of synaptic adaptation and habituation to standard stimuli. In a state of habituation novelty detectors are inactive. However when feature detectors signal change in response to a deviant stimulus, then the novelty detectors respond and MMN is evoked. Deviant repetition results in adaptation and habituation, as the deviant auditory stimulus

information is incorporated into the neuronal model. This results in a gradual reduction of the mismatch between the neuronal model and the presenting stimulus, and provokes a corresponding decline of MMN. This system can be equated with the comparison process of the model comparator paradigm.

There is one unresolved issue regarding application of Sokolov's (1975) orienting response theory to MMN. In Sokolov's model comparator system of the orienting response, the orienting response is provoked in response to a new novel stimulus, which may not signal a change in a series of homogenous stimuli. However the MMN comparison system consists of auditory cortex cells which are sensitive only to short inter-stimulus interval changes, and which do not respond to the first in a series of stimuli. One possible explanation is that auditory change detectors are inhibited at rest, but reversal of this inhibition follows presentation of the first stimulus in a series. Reversal of inhibition may render the change detector active, and sensitive to any change in stimulation (Sams et al., 1991). This addition to Sokolovs' model comparator theory reconciles the differences, and provides a plausible account of MMN.

Sams, Alho, and Naatanen (1984) found evidence supporting the constructs of the model comparator theory when they detected gradual attenuation of MMN in response to repeated deviant presentation. They recorded ERPs to four tones: to single deviant tones of low (10%) probability following standards of high (90%) probability; to a second repetition of the deviant tone immediately following the first deviant; and to the first and second standard

tones following presentation of both one deviant and of two consecutive deviant tones. They found MMN to be evoked by all four tones. MMN to the first deviant was of the largest amplitude, while MMN elicited in response to the second repetition of the deviant was of smaller amplitude. MMN to the standard tones was small when it followed only one deviant tone, but larger when it followed two deviant tones. The MMN detected in response to the second standard following presentation of the deviant was reduced compared to the first standard.

The experiment of Sams et al. (1984) provides support for the model comparator theory of MMN. It demonstrates the existence of both a strong short term habituation effect of the MMN generator process, as MMN accompanies any stimulus change, and also shows the rapid decay of previous neural templates. Reduced MMN to the second repetition of both the deviant and standard stimuli plausibly illustrates the gradual consolidation of traces by incorporation of new information as these stimuli are repeated. This is consistent with model comparator theory in which gradual reinforcement of these traces causes them to usurp prior sensory memory stores, resulting in the establishment of a new, habituating neuronal template.

The model comparator theory regards MMN as a cortical registration of change which occurs as a consequence of neural detection of a difference between the current sensory stimulus information and the neuronal template of prior static stimuli which is contained in the auditory memory. The subsequent issue regards

whether this process is performed automatically or is contingent upon voluntary direction of attention to the change.

4. Automatic processing: early or late selection?

MMN has been one research tool which has been used to distinguish those cognitive processes which are voluntary and contingent upon selective attention, from those which are automatic and subject to preattentive processing.

Early selection theories of attention assert that only superficial, sensory analysis is completely automatic. Subsequent selection of stimuli for information processing is thought to be controlled and contingent upon attention, whereas unselected stimuli are processed no further than the level of basic sensory characteristics. However research has detected information processing of salient information in unattended channels (Moray, 1959). Consequently it has been suggested that information processing can occur prior to the selection of stimuli and channelling of attention for conscious processing.

Naatanen (1988) discriminates between voluntary attention, where attention is directed toward a stimulus by conscious, purposeful control by the organism, and involuntary attention, in which attention is attracted by the salience of the stimulus, leading to it's intrusion upon attention. This latter concept of involuntary attention formed the basis for the evolution of late selection theories of attention (Naatanen, 1988) which regard perceptual analysis of stimuli as automatic, irrespective of the voluntary direction of

attention. According to this model, selection of stimuli for controlled processing occurs only after sensory analyses are represented in sensory memory. Consistent with this Naatanen (1985) and Sams et al. (1984) propose that the MMN neural traces in the auditory cortex are the anatomical locus of the auditory sensory memory. This sensory memory is a short duration, large capacity store which is independent of attention. It stores templates of sensory information including, pitch, intensity, location, and duration. Thus late selection theories attribute a higher degree of automaticity of information processing than do early selection theories.

Graham and Hackley (1991) differentiate three levels of automaticity of processing which can be used to differentiate ERP components; exogenous, mesogenous, and endogenous. Exogenous components of the ERP are processed completely involuntarily, processing is contingent upon stimulus characteristics. In this category processing is strongly automatic, it is neither facilitated nor inhibited by the direction of selective attention. Exogenous components are thought to occur less than approximately 250 milliseconds (ms) after stimulus presentation.

The processing of mesogenous components is involuntary, but can be influenced by selective attention. Processing is partially automatic, as analysis can be enhanced or inhibited by attention being diverted toward or away from the stimulus. The processing of endogenous components, however, is completely controlled and voluntary. Endogenous components are thought to occur only in the presence of attention, and thus are contingent upon voluntary,

directed attention. Endogenous components of the ERP are thought to occur after approximately 250 ms following stimulus presentation and indicate information processing of the sensory stimulus information including stimulus encoding, comparison, evaluation, categorisation, and representation in memory (Empson 1986). The temporal demarcation of 250 ms is only approximate, and is not appropriate for discriminating exogenous from endogenous components.

There has been much debate over whether MMN is evoked only when attention is directed toward the evoking stimulus, or whether it can also be evoked when the subject's attention is strongly diverted elsewhere. Contemporary research favours the concept of MMN as mesogenous, occurring both in the presence and absence of attention (Paavilainen, Tiitinen, Alho, & Naatanen, 1994).

5. Mismatch negativity and attention

The resource allocation model of attention can be used to investigate the attentional status of MMN. The resource allocation model regards attentional processing resources as limited. Allocation of attentional resources to one pathway has the effect of enhancing performance in that attended pathway. However due to reduced attention being available to other pathways, processing efficiency in those pathways is reduced (Hillyard & Hansen, 1986). According to the resource allocation model, if MMN were endogenous then MMN amplitude would be expected to show differences between attended and non-attended conditions.

The role of attention in MMN processing can be calculated by firstly measuring MMN. This is achieved by averaging ERPs recorded in response to deviant and standard stimuli, and then subtracting the averaged waveform in response to common stimuli from the averaged waveform in response to the deviant stimuli. This will yield a measure of MMN at approximately 150 - 250 ms post stimulus presentation. By manipulating attention two further specific ERPs can be obtained from the same channel; one in the attending condition where attention is focussed upon the channel, and one in the non-attending condition, where attention is strongly focussed upon another channel. Comparison of the ERP waveform obtained in the attended condition, from that obtained in the non-attended condition may reveal identical ERPs regardless of attentional manipulations. This would indicate that attention had no effect upon the MMN response, and that channels do not compete for attention when processing MMN. Consequently it would be concluded that MMN is an exogenous component of the ERP. Alternatively subtraction of the waveform in the attended condition from that of the non-attended condition may show a difference waveform. This would indicate the existence of a differential effect of attentional manipulations. The presence of a difference waveform would confirm that when attention was focussed upon one channel, processing efficiency in other channels was reduced, and that MMN is either endogenous or mesogenous in nature.

A review of recent research reveals contention over the relationship between MMN and attention. One position (Naatanen, 1988; 1991) advocates that, consistent with the late selection theory

of information processing (Naatanen, 1985), neural detection of a physical mismatch and MMN occur automatically in response to stimulus mismatches (Naatanen & Gaillard, 1983). Thus Naatanen (1982) proposes that MMN is a preconscious physiological representation of stimulus change. According to Naatanen (1985), the role of MMN may be the attraction and channelling of attention to the change in unattended stimuli. The attraction of attention would then allow stimulus selection, representation in memory, and semantic processing in memory.

The assertion of Naatanen and Gaillard (1983) of the automaticity of MMN, suggests that physical encoding is conducted to an equal degree, regardless of whether attention is focussed upon the mismatched stimulus or elsewhere. Thus Naatanen and Gaillard view MMN as being completely exogenous. Consistent with this Naatanen and Gaillard (1983) and many other researchers (Alho, Lavikainen, Reinikainen, Sams, & Naatanen, 1990, Alho, Woods, & Algazi, 1994) have reported no change in MMN when attention was manipulated, and that auditory tones are fully analysed even in the absence of attention (Paviliainen et al., 1994).

However other research has reported that MMN is mesogenous. This position supports the early selection theory of information processing in which sensory processing is automatic, and selection of stimuli for comparison allowing detection of a mismatch occurs later, following the channelling of attention to this stimuli. Attended stimuli are viewed as being more accurately detected, discriminated, and recalled than are non-attended stimuli.

Thus it has been proposed that physical mismatch detection, accuracy, and efficiency will be greater when conducted under conditions of attention. Consistent with this hypothesis Woldorff, Hackley, and Hillyard (1991) found that MMN amplitude is vulnerable to attenuation when attention is diverted, and enhancement when attention is focussed upon the eliciting stimulus. When Woldorff et al. (1991) used frequency deviants attentional manipulation produced no difference waveform suggesting that attention does not modulate MMN processing of frequency changes (Naatanen, 1991; Alho et al., 1994). However when intensity deviants were used, attentional manipulation did produce a difference waveform suggesting that attenuation of MMN can occur when attention is strongly diverted away from an intensity deviant. Thus it appears that the mesogeny or exogeny of MMN is dependent upon the sensory parameter of change.

Naatanen (1991) contended that an attentional effect on MMN may not necessarily indicate a reduction of processing at an early sensory level. Although the research of Woldorff et al. (1991) was interpreted as indicating that attention affects the efficiency of sensory processing of intensity changes, Naatanen asserts that equally the MMN amplitude reduction may be due to a post sensory influence at a later stage of processing or comparison. He supports this with the observation that only intensity deviants but not frequency deviants were affected by attentional modulation. If the interference occurs at an early sensory level then all sensory parameters of deviance would be expected to result in a difference waveform indicative of attentional modulation, and therefore of the

mesogeny of MMN. Accordingly it would be predicted that, if attention does effect the sensory processing of stimuli, there must exist a small magnitude of frequency deviation at which even a small MMN is only evoked in the presence of attention, but is extinguished in it's absence. However Paavilainen et al. (1994) have shown that even the smallest frequency deviation (3%) which reliably evokes MMN is not vulnerable to attentional modulation. Therefore it appears that under no conditions can attention affect the sensory processing of frequency MMN, and furthermore that there are no conditions under which the frequency MMN is completely extinguished by the withdrawal of attention. Thus an alternative explanation for the attentional modulation of the intensity MMN is warranted. Naatanen maintains the exogeny of MMN, and offers an alternative explanation for the influence of attention upon MMN evoked by intensity deviants.

Naatanen (1991) has proposed the existence of parameter specific MMN generators. These specific MMN generators may be sensitive to any one sensory characteristic of an auditory stimulus, such as intensity, frequency, duration, or inter-stimulus interval. Naatanen maintains that sensory analysis and comparison of sensory input with the existing neuronal template is automatic. He attributes attenuation to suppression of specific MMN generators, rather than to the suppression or enhancement of antecedent exogenous sensory analysis (Naatanen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). According to this proposal, attention suppresses or enhances only the response of the auditory cortex novelty detectors. This is supported by findings which suggest that stimulants increase

MMN amplitude (Pietrowsky et al., 1989) and that sedatives decrease MMN amplitude. (Born, Kern, Fehm-Wolfsdorf, & Fehm, 1987). These drugs are reported to affect attention and arousal, and thus effects upon MMN amplitude were posited to occur as a consequence of attention, thereby proving the endogeny of MMN. According to the model of Naatanen et al. (1993), reductions in amplitude can be attributed not to attentionally reduced sensory processing but to attentionally modulated inhibition of MMN generation.

Support for Naatanens' theory derives from research which has reported differences between MMN elicited by frequency, duration, and intensity deviants (Paavilainen et al., 1991). Paavilainen et al. (1991) also hypothesised the existence of functionally and anatomically separate sensory memory processes for specific auditory attributes. The existence of these parameter specific auditory memory processes is confirmed by the discovery of anatomically separate sites for different deviants which have been detected in magnetoencephalographic studies (Levanen, Hari, McEvoy, & Sams, 1993). Thus the theory of Naatanen of reduction, not of sensory processing, but of MMN generators is consistent with some current research and suggests that MMN may be exogenous.

In summary, Woldorff et al. (1991) assert that MMN is mesogenous. The sensory information processing of MMN is partially automatic, but is influenced by attention, resulting in the suppression or enhancement of early sensory processing. Naatanen (1991) argues that MMN is completely exogenous. The sensory

processing of MMN is automatic and operates independently of attention. Observed suppression or enhancement of MMN is a consequence of inhibition or excitation of the action of neuronal novelty detectors. While Naatanens' theory is a plausible explanation of the MMN dilemma, his theory remains to be tested. Drugs which depress neural activity such as alcohol and the minor tranquillisers may provide a means by which to elucidate this.

6. Alcohol and event-related potentials

Alcohol is a central nervous system (CNS) depressant similar to anaesthetics, which acts via the midbrain reticular activating system. High and low doses of alcohol have been reported to show contrary neurochemical and behavioural effects (Salamy & Williams, 1973).

The effects of alcohol upon the ERP are complex. Interpretation of research is further complicated by the differential effect of different doses of alcohol upon information processing, attention, and ERPs. Increasing doses of alcohol have been reported to show a linear effect on the disruption of information processing and psychomotor performance (Hindmarsh, Bhatti, Starmer, & Mascord, 1992; Morland, Setekliev, Haffner, Stromsaether, Danielson, & Wethe, 1974; Liljequist, Palva, & Linnoila, 1979).

Acute doses of alcohol have been observed to consistently impair information outputting operations such as response selection and organisation, rather than stimulus inputting operations such as stimulus preprocessing and encoding (Tharp, Rundell, Lester, &

Williams, 1974). However early components of the ERP have been reported to show an effect of large doses of alcohol. These effects were dependent upon whether attention was directed toward the evoking stimulus, or focussed elsewhere. N100 amplitude has been reported to be reduced for attended deviants, but not for non-attended deviants (Krull, Smith, & Parsons, 1994) and late components such as the P300 show a contrary effect being reduced for non-attended deviants, but remaining the same for attended deviants in the presence of alcohol (Campbell & Lowick, 1987).

Attenuation of the early components of the ERP (N100, P200) at high blood alcohol contents is attributed to generalised CNS depression (Salamy & Williams, 1973). However findings of reduced amplitudes to attended stimuli but not to non-attended stimuli indicate a differential effect of alcohol dependent upon attention and could be interpreted as indicating that alcohol reduces the efficacy of processing and comparison as a consequence of reduced attentional resources. However other studies have not supported this theory. Porjesz and Begleiter (1993) reported reduced P300 amplitude to both attended and non-attended stimuli under the influence of high doses of alcohol.

Low doses of alcohol are also reported to affect P300 (Oscar-Berman, 1987; Porjesz & Begleiter, 1993). However the effects of attention were equivocal in these studies therefore they provide no support for the theory that alcohol reduces attentional resources.

7. Mismatch negativity and alcohol

Realmuto, Begleiter, Odencrantz, and Porjesz (1993) found reduced amplitude and increased latency of N200 and MMN in response to unattended deviants in chronic users of alcohol compared to controls. Based on the assumption that N200 indexes discrimination difficulty, increased latency suggests that alcoholics have deficits in stimulus evaluation processes compared to controls. N200 and P300 data suggest that alcoholics experience more difficulty evaluating the significance of a stimulus than controls. This can be interpreted as a deficit in formation of neuronal templates resulting in the deviant stimulus failing to produce a MMN response equal to controls. Furthermore this supports the hypothesis that alcohol affects attentional resources. The chronic effects of alcohol, however can be generalised to acute effects only with caution.

These studies suggest that high doses of alcohol reduce attentional resources. If, as suggested, alcohol exerts it's amplitude reductions due to reduced attentional resources and reduced efficacy of processing, then its effect on MMN will reveal whether MMN is exogenous or endogenous.

8. Mismatch negativity, alcohol, and attention

If alcohol reduces attentional resources and consequently reduces the amplitude of endogenous components, then if MMN is an endogenous component, alcohol should produce a decrease in MMN when attention is strongly diverted from the eliciting stimulus. This would be manifested as a difference waveform.

Alternatively if MMN is an exogenous component, and independent of attention, then alcohol would not be expected to produce a decrease in amplitude when attention is strongly diverted away from the deviant stimulus. However a small reduction in amplitude would be expected given the generalised depressive effects of alcohol.

Temazepam also is known to affect attentional resources and may also, along with alcohol contribute to testing Naatanens' theory.

9. Mismatch negativity and temazepam

Temazepam is a minor tranquilliser from the benzodiazepine group. Benzodiazepine effects are dose dependent. Low doses of 15-30 mg have anxiolytic effects, producing hypnosis, sedation, and muscular relaxation (Craig & Stitzel, 1982), while increasingly higher doses induce hypnosis and stupor (Goodman Gilman, Goodman, Rall, & Murad, 1985). Benzodiazepine neural receptors are widely distributed, primarily in the phylogenetically older areas of the CNS such as the pons and medulla (Davies, 1990). Benzodiazepine anxiolytic effects can be attributed to the existence of a substrate which is subject to GABA-ergic inhibitory control (Gray, 1982; 1983).

Generally benzodiazepines have been found to result in reduced psychomotor speed of simple repetitive tasks, learning, and memory, but there is little indication of a decrement to well established higher mental functions (McNair, 1973) at regular doses 15 - 30 mg (Lerder, 1983).

The neural effects of temazepam are observed to be primarily frontal and central, with little or no posterior effect. Consistent with the anxiolytic effects, benzodiazepines reduce the amplitude of cortical somatosensory event-related potentials and increase the latency of endogenous components (Goodman Gilman et al., 1985). The effect of benzodiazepines upon endogenous components only, is suggestive of an effect upon attention.

10. Mismatch negativity, temazepam, and attention

Research into early components of the ERP (P100 and P200) has reported that they are not subject to the influence of temazepam (Declerk, 1993). However low doses of temazepam (10 mg), have been reported to reduce the amplitude and increase the latency of the P300 component, signifying an effect upon endogenous cognitive processes (Martin et al., in press). This suggests that in addition to the anxiolytic and sedative effects of temazepam there is an effect upon attention. This attentional effect is thought to be a reduction in the ability to alert the brain to stimuli, and is mediated by the reticular activating system.

Thus it may be concluded that the effects of temazepam are endogenous, affecting stimulus evaluation, response organisation, and execution, but not influencing early sensory processes such as stimulus encoding, schematic updating, information transmission, and processing space. Therefore it has been proposed that low doses of temazepam reduce attentional resources (Martin et al., in press). Alternatively the reduction of attentional resources may be due to GABA mediated CNS depression.

The effects of temazepam upon attention may provide an opportunity to reveal the exogenous or endogenous nature of MMN. If temazepam affects only attentive processes, then it can be inferred that if temazepam causes attenuation of MMN, then this would indicate that MMN is an endogenous component. Alternatively, if temazepam causes no attenuation of the evoked potential in response to deviant stimuli, and no decrement in MMN, then it may be concluded that MMN is a preattentive component.

In this way temazepam may be used as a tool to investigate the exogeny, mesogeny, or endogeny of MMN, through revealing whether MMN is subject to the effects of attention. The remaining issue regards the effect upon MMN of alcohol and temazepam in combination.

11. Mismatch negativity, alcohol, temazepam, and attention

Because alcohol and temazepam affect attentional resources, both these drugs are expected to affect only endogenous components which operate in the presence of attention. Therefore if MMN is endogenous, then both alcohol and temazepam individually, would be expected to show an effect upon MMN. Specifically a reduction in the amplitude of this ERP would be expected. However the combined effect of these drugs remains to be established.

An additive effect occurs where the effects of variables are incremental, and can be attributed to both variables singly. An interactive effect occurs where the total effect is greater than the

individual effect of either variable alone, suggesting that the total effect is a product of the interaction between the variables.

No research has been conducted which tests the effect upon MMN of both alcohol and temazepam in combination. However the combination of alcohol and other benzodiazepines has been shown to generate interactive effects on cognitive functions (Morland et al., 1974; Liljequist et al., 1979). Interactive effects of benzodiazepines and alcohol have been reported in which alcohol potentiated the effects of midazolam (Subhan & Hindmarch, 1983) and lorazepam (Kerr, Fairweather, Mahendran, & Hindmarch, 1992) upon a range of functions.

In addition P300 research can reveal possible effects of both alcohol and temazepam upon MMN. Similarly to MMN, P300 amplitude is reduced by high doses of alcohol, but at this dose an interactive effect occurs between temazepam and alcohol, in which alcohol and temazepam in combination reduce P300 amplitude more than the combined effect of either drug alone (Martin, Declerk, & Guidici, 1993).

Although no research is available to reveal the combined effect of low doses of alcohol and temazepam upon MMN, the combined effect of other benzodiazepines and alcohol has shown an interactive effect upon information processes and ERPs. Therefore if MMN is an endogenous component an interactive effect of alcohol and temazepam upon MMN would be predicted in which alcohol and temazepam together reduce MMN amplitude to a greater degree

than the sum of the separate effects of each drug. This would be indicated by a difference waveform occurring in the attention condition which would be larger than the difference waveform of either drug alone.

12. Summary and conclusions

The literature regarding the MMN component of the event-related potential has been reviewed. The model comparator theory was presented and, with some elaboration, was found to provide an accurate and useful model of this component. The automatic or controlled nature of mismatch negativity processing was reviewed and the debate regarding the role of attention was critically analysed. Two major positions have been advocated and both appear viable, however they remain to be tested to establish which model provides a legitimate explanation of mismatch negativity. Temazepam and alcohol were discussed in reference to their effects upon attention. Both temazepam and alcohol, individually, and in combination, were proposed to offer an instrument for resolving the debate regarding the attentional dependence or independence of mismatch negativity. Also the additive or interactive effects upon MMN of alcohol and temazepam were speculated upon. Research of other cognitive processes, and of the P300 component suggests that an interactive effect could be anticipated if MMN is endogenous.

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THE EFFECTS OF ALCOHOL AND TEMAZEPAM UPON MISMATCH NEGATIVITY

Journal Article

CONTENTS

ABSTRACT

The mismatch negativity (MMN) component of the auditory event-related potential (ERP) is elicited by a deviant stimulus following a sequence of homogenous stimuli. MMN has been the subject of debate regarding its exogenous or endogenous nature. Alcohol and temazepam have been proposed to affect attentional resources, and thus by manipulating subjects' attention and these drugs, the attentional status of MMN would be elucidated. Standard and deviant auditory stimuli were presented to subjects (n=12) who completed eight conditions in a 2 (task: read/count) x 2 (alcohol yes/no) x 2 (temazepam yes/no). Recordings of electroencephalographic responses to standard (1000 Hz) and deviant (1200 Hz) stimuli were taken from Fz, Cz, and Pz. Averaged difference waveforms were calculated for each site in each condition. A Negative difference (deviant - standard) was recorded in both attentional conditions. No effect of attention was recorded at Fz, the principal site at which MMN manifests, leading to the conclusion of the preattentive nature of MMN. Temazepam was found to affect the endogenous P3 but not the Nd. Alcohol was found to affect the Nd but not the P3, suggesting that the effects of low doses of alcohol are not purely upon attention.

MMN is a frontally recorded negative component of the auditory ERP. It is recorded at approximately 200 ms post presentation of a physically deviant stimulus following a consecutive sequence of physically homogenous stimuli. The nature of this deviance may be any physical parameter such as changes in pitch (Naatanen, 1986), intensity, duration (Naatanen, 1982), or unexpected early presentation (Novak, Ritter, & Vaughan, 1992). MMN is closely followed by the P3 component which has been associated with the cognitive processes of stimulus recognition and classification (Hillyard & Kutas, 1983).

The cognitive mismatch process has been depicted in terms of the model comparator theory (Sams, Kaukoranta, Hamalainen, & Naatanen, 1991). The model comparator theory regards MMN as a cortical registration of change which occurs as a consequence of neural detection of a difference between the current sensory stimulus information and the neuronal template of prior static stimuli which is contained in the auditory memory. Currently debate exists regarding whether this process is performed automatically (Naatanen & Gaillard, 1983) or is a conscious process which is contingent upon the voluntary direction of attention to the change (Woldorff, Hackley & Hillyard, 1991).

Two levels of automaticity of processing are proposed: exogenous and endogenous. Exogenous

components of the ERP are processed completely involuntarily; processing is neither facilitated nor inhibited by the direction of selective attention. The processing of endogenous components, however, is thought to occur only in the presence of attention, and thus is contingent upon voluntary, directed attention (Graham & Hackley, 1991) .

Naatanen (1988) has posited that MMN is an exogenous change detection mechanism which is precedent to attention being channelled to the changed stimulus. According to this perspective, selection of stimuli for controlled processing occurs only after sensory analyses are represented in sensory memory. Attraction of attention would then allow stimulus selection, representation in memory, and semantic processing such as stimulus recognition and classification which are associated with the endogenous P3 (Hillyard & Kutas, 1983). In accordance with this model Naatanen (1985) and Sams, Alho, and Naatanen (1984) propose that the MMN neural traces in the auditory cortex are the anatomical locus of the auditory sensory memory. This sensory memory is a short duration, large capacity store which is independent of attention.

Consistent with the proposed exogeny of MMN, Naatanen and Gaillard (1983) and many other researchers (e.g. Alho, Lavikainen, Reinikainen, Sams, & Naatanen, 1990; Alho, Woods, & Algazi, 1994) have

reported no change in MMN when attention was manipulated, and that auditory tones are fully analysed even in the absence of attention (Paviliainen, Tiitinen, Alho, & Naatanen, 1994).

However Woldorff, Hackley, and Hillyard (1991) assert that MMN is influenced by attention. According to the resource allocation model of attention (Hillyard & Hansen, 1986), direction of attention to one channel enhances processing in that channel, but reduces the efficiency of processing in other channels. Consistent with this hypothesis Woldorff et al., (1991) found that MMN amplitude is vulnerable to attenuation when attention is diverted, and enhancement when attention is focussed upon an intensity deviant stimulus. This suggests that attenuation of MMN can occur when attention is strongly diverted away from an intensity deviant. Thus it appears that the relationship between attention and MMN is complex.

Research which has manipulated attention has been unsuccessful in unequivocally identifying MMN as either exogenous or endogenous. An additional method of measuring the effect of attention upon MMN is to test the effect upon MMN of drugs which reduce attentional resources. Alcohol and temazepam are both drugs which are posited to reduce attentional resources, and thus offer the opportunity to resolve the exogeny or endogeny of MMN.

Alcohol is a central nervous system (CNS) depressant similar to anaesthetics (Salamy & Williams, 1973). Components of the auditory ERP have been reported to show an effect of large doses of alcohol. Reports of reduced amplitudes to attended stimuli but not to non-attended stimuli suggest that alcohol reduces the efficacy of processing and comparison as a consequence of reduced attentional resources. This suggests that high doses of alcohol influence only endogenous components of the ERP.

If alcohol does attenuate the amplitude of endogenous ERP components as a consequence of reduced attentional resources, then it's effect on MMN will reveal whether MMN is exogenous or endogenous. If MMN is an exogenous component, and independent of attention, then alcohol would not be expected to produce a decrease in amplitude when attention is strongly diverted away from the deviant stimulus. Although a small reduction in amplitude may be expected given the generalised depressive effects of alcohol (Salamy & Williams, 1973). However if MMN is endogenous then a difference waveform would be expected, in which attention enhanced MMN amplitude while the absence of attention suppressed MMN amplitude under the effects of alcohol.

Temazepam also is known to affect attentional resources and may also assist in discovering the

endogeny or exogeny of MMN. Temazepam is a minor tranquilliser from the benzodiazepine group which has an hypnotic, anxiolytic effect (Goodman Gilman, Goodman, Rall, & Murad, 1985). The neural effects of temazepam are observed to be primarily frontal and central, with little or no posterior effect. Research into early components of the ERP (P100 and P200) has reported that they are not affected by temazepam (Declerk, 1993). However benzodiazepines are reported to reduce the amplitude and increase the latency of the P300 (Martin, Nichols, Mills, & Siddle, 1993). The effect of benzodiazepines upon endogenous components only, is suggestive of an effect upon attention, and suggests that low doses of temazepam may reduce attentional resources (Martin et al., 1993).

The effects of temazepam upon attention may provide an opportunity to reveal the exogenous or endogenous nature of MMN. If temazepam affects only attentive processes, then it can be inferred that if temazepam causes attenuation of MMN, then MMN is an endogenous component. Alternatively, if temazepam causes no attenuation of the evoked potential in response to deviant stimuli, and no decrement in MMN, then it may be concluded that MMN is an exogenous component. However some attenuation would be expected given the generalised CNS depressive effect of temazepam (Goodman Gilman et al., 1985).

Because alcohol and temazepam effect attentional resources, both these drugs are expected to affect only endogenous components which occur in the presence of attention. Therefore if MMN is endogenous, then both alcohol and temazepam individually would be expected to show a reduction in the amplitude of this component. However the combined effect of these drugs remains to be established.

No research has been conducted which tests the effect upon MMN of both alcohol and temazepam in combination. However the combination of alcohol and other benzodiazepines has been shown to generate interactive effects on cognitive functions (Morland, Setekliev, Haffner, Stromsaether, Danielson, & Wethe, 1974; Liljequist, Palva, & Linnoila, 1979; Subhan & Hindmarch, 1983; Kerr, Fairweather, Mahendran, & Hindmarch, 1992). This suggests that alcohol and temazepam may have an interactive effect upon mismatch detection and MMN amplitude.

In addition P300 research can reveal possible effects of both alcohol and temazepam upon MMN. P300 amplitude is reduced by high doses of alcohol, but at this dose an interactive effect occurs between temazepam and alcohol, in which these two drugs reduce P300 amplitude more than the combined effect of either drug alone (Martin, Declerk, & Guidici, 1993).

Although no research is available to reveal the combined effect of alcohol and temazepam upon MMN, the combined effect of other benzodiazepines and alcohol has shown an interactive effect upon information processes and ERPs. Therefore if MMN is an endogenous component an interactive effect of alcohol and temazepam upon MMN would be predicted in which alcohol and temazepam together reduce MMN amplitude to a greater degree than the sum of the separate effects of each drug. This would be indicated by a reduced difference waveform occurring under the influence of these drugs when attention was focussed upon the evoking stimulus. In this way both alcohol and temazepam may be used as a tool to investigate the exogeny or endogeny of MMN, by revealing whether MMN is subject to the effects of attention.

The aim of this experiment is to investigate the exogenous or endogenous status of MMN. In order to discover its attentional status, MMN will be measured under conditions of attention and non-attention. If the amplitude difference in the attention condition is significantly different from the amplitude difference in the non-attending condition then this will indicate an effect of attention and show that MMN is endogenous. If, however, MMN is equal under both conditions, then this will show that MMN is exogenous, and impervious to the effects of attention. Attentional manipulation will occur by requiring subjects to focus attention either upon the

evoking stimulus or elsewhere, and by reducing attentional resources using both alcohol and temazepam.

It is hypothesised that MMN will be elicited in response to deviant tones, primarily at Fz and Cz sites. It is predicted that P3 will be evoked in the attentional conditions primarily at Cz and Pz. Consistent with the model of Woldorff et al. (1991), it is expected that MMN will be affected by attention. Consequently MMN is expected to produce greater amplitude differences (deviant - standard) in the attending conditions, compared to the non-attending conditions. It is predicted that, as alcohol and temazepam reduce attentional resources, that these drugs will reduce MMN compared to the no drugs conditions. Furthermore it is anticipated that, as alcohol and temazepam are proposed to have an interactive effect upon endogenous components of the ERP, that alcohol and temazepam in combination will reduce MMN more than the additive effects of each drug.

METHOD

Subjects

Twelve experimentally naive female undergraduates, between the ages of 18 and 27 (mean = 24) years completed the experiment. An homogeneous subject group of females of this age was used as this age group is reportedly more sensitive to stimulus deviance

(Czeigler, Csibra, & Csontos, 1982). In addition the P3 peak has been reported to show differential latency in older subjects, reducing the effectiveness of the averaging of this component (Verleger, Neukter, Komf, & Nieregge, 1991). Medical history questionnaires (Appendix A) were completed to ensure that subjects had normal hearing and acuity, no family history of alcoholism or drug use, and that subjects were neither heavy smokers or drinkers, were not currently on medication, and had no previous history of concussion or brain damage. Participant consent forms (Appendix B) were also completed. The experiment received approval from the University of Tasmania Human Ethics Committee.

Physiological recording

Electroencephalographic (EEG) activity was recorded using a Grass Neurodata Model 12 Acquisition System and IBM compatible 486 computer. The EEG was digitised at a rate of 500 Hz for a 660 ms epoch beginning 60 ms prior to stimulus onset and terminating 600 ms post stimulus onset. The high frequency cut off for the EEG recordings was 30 Hz and the time constant was 15 ms. Electrodes were connected to the subject's scalp using an Electro skull cap in accordance with the International 10/20 placement system (Jasper, 1958). Measurements were taken from Fz, Cz, and Pz recording sites, with the right ear serving as a reference point. Electrode impedance was kept below 5 kΩ. Electro-

occulographic (EOG) recordings were taken from electrodes which were attached above and below the right eye of the subject. All EEG records with EOG activity exceeding 70 μV were excluded from computer averaging to ensure that a pure measure, free from contamination by eye movement was obtained.

Design

All subjects were tested in counterbalanced conditions in a 2 temazepam (yes/no) x 2 alcohol (yes/no) x 2 attention (counting/reading) x 3 site (Fz/Cz/Pz) fully closed, repeated measures factorial design.

The independent variables were the two attention conditions of counting and reading, the four drug conditions of temazepam and placebo, placebo alone, alcohol and placebo, and alcohol and temazepam, and the three electrode sites. These variables were manipulated and measures taken of the dependent variable of mean difference amplitude for MMN and P3.

Procedure

Subjects attended four sessions during which they participated in one of the four drug conditions, and both task conditions of count/read. The task conditions were held consecutively during each session and the order of count and read conditions was counterbalanced. Each session was scheduled a minimum of three days

apart and each subject attended no more than two sessions per week to ensure that no residual drug contamination remained from the previous session.

Subjects were prohibited from eating or drinking caffeinated or alcoholic drinks for a period of four hours prior to the experiment to reduce interference in drug absorption. Subjects attended all sessions in the late afternoon and evening. They were driven home at the completion of each session, and advised not to consume alcohol or to drive a car in the 24 hours following the experiment.

Upon attendance at the laboratory, subjects completed a medical questionnaire and consent form. Subject's blood pressure and blood alcohol content (BAC) were measured. Body weight was also measured to enable calculation of the appropriate quantity of alcohol required for individual subjects to reach a level of 0.04% BAC (0.82 ml/Kg). Subjects were then given four drinks containing alcohol or a placebo dependent upon the condition. Drinks contained orange juice, vodka, and peppermint water to disguise the alcohol and placebo conditions. These drinks were taken over a twenty minute period and a total of forty minutes was allowed for the BAC to reach the desired level of 0.04% prior to commencement of the experiment. Ten mg temazepam (NORMISON) or a placebo (Breathless Garlic, 2mg) was also taken 30 minutes prior to commencement to allow

optimal drug effect. Breathless garlic was selected for use as the placebo as the shape and texture of the pill was identical to that of NORMISON. Whilst waiting for the drugs to be absorbed subjects were fitted with the electrode skull cap and electrodes, and blood pressure was checked. Subjects were then seated comfortably in a sound attenuated room, and BAC was measured to ensure that the appropriate level was reached.

The stimuli were presented in four blocks (500 tones per block) in each of the task conditions. The duration of each block was eight minutes followed by a short break of about 30 seconds between blocks. The tones were generated by an IBM compatible 486 computer, and presented binaurally through headphones. Standard tones were 50 ms in duration (rise time 10 ms) at 75 dB intensity, and pitch 1000 Hz. Deviant tones were 50 ms duration (rise time 10 ms), 75 dB intensity, and 1200 Hz. Deviant tones were randomly distributed and composed 10% of the total tones presented. All tones were separated by an inter-stimulus interval (ISI) of 1000 ms. A minimum number of 5 standard tones preceded each deviant.

Subjects were given standardised instructions (Appendix C) to remain alert and to attempt to keep eye and body movement to a minimum. Prior to the counting condition subjects were requested to attend to the auditory stimuli and count the deviant tones and to

report the total number of deviant tones counted at the end of the session. Prior to the reading condition subjects were instructed to ignore the auditory stimuli and read the text provided to facilitate completion of a comprehension test at the end of the session. Headphones were placed upon the subjects head, the standardised text was provided for those subjects in the reading condition, and subjects were presented with auditory tones.

Following task conditions the subjects were required to complete either the comprehension test (Appendix D) or to report the number of deviant tones counted dependent upon the task condition. Following this the subject's BAC was recorded and subjects were again given the initial instructions to remain still and either read or count for a second set of four blocks of 500 tones.

At the completion of the second task condition in each session, subjects were asked either to complete the comprehension test or report the number of deviant tones counted, BAC (Appendix E) and blood pressure were measured, and subjects were asked to complete separate subjective sedation and intoxication ratings (Appendix F). Subjects remained in the laboratory and were provided with a meal before being driven home.

Data Analysis

ERPs were recorded for the deviant stimuli and the standard stimuli. The standard stimuli analysed comprised the tones directly preceding the deviant during stimulus presentation.

Grand mean difference waveforms for each condition at each site were calculated by an IBM compatible 486 computer. Difference waveforms were calculated by subtracting the averaged amplitude in response to the standard from that of the deviant. The difference waveform was used to present the results to allow comparability with the findings of other researchers who have used this method of presentation (e.g. Woldorff et al., 1991; Naatanen, 1991; Naatanen, Jiang, Lavikainen, Reinikainen, & Paavilainen, 1993; Hillyard & Hansen, 1986).

Single subject MMN and P3 amplitudes were measured from all electrodes as the mean amplitude during a period plus and minus 25 ms around a peak latency (Tervaniemi, Saarinen, Paavilainen, & Naatanen, 1993). Peak latency was defined as the maximum amplitude within a latency window. The epoch for each component was derived from the grand mean averages. For the MMN component the peak latency was between 100-300 ms, and for the P3 component the peak latency was between 200-400 ms.

Data (Appendix G) for each of the MMN and P3 difference components were analysed separately using a Statistica package on an IBM compatible 486 computer. A four-way 2 temazepam (yes/no) x 2 alcohol (yes/no) x 2 attention (counting/reading) x 3 site (Fz/Cz/Pz) analysis of variance with repeated measures tested the main effects and interactions. A significance level of $p<.05$ following Greenhouse-Geisser correction was met for all main effects and interactions. Student Newman-Keuls (SNKs) tests, for which the significance level was set at $p<.05$ were used to test for significance of differences between individual means where appropriate (Appendix H).

The performance data from the counting and comprehension tests was collated (Appendix I) and tested separately with a two-way (temazepam: yes/no, alcohol: yes/no) ANOVA (Appendix J).

RESULTS

Subjective sedation and intoxication ratings (Appendix K) completed in all conditions showed that subjects were aware when they were under the influences of a drug or alcohol. In the placebo condition no subjects rated themselves as feeling intoxicated although 2 rated themselves as slightly sedated. In the alcohol condition 11 subjects rated themselves as moderately intoxicated, and 8 subjects rated themselves

as slightly sedated. In the temazepam condition 9 subjects rated themselves as slightly sedated, and 5 subjects rated themselves as slightly intoxicated. In the combined alcohol, temazepam condition 9 subjects rated themselves as moderately sedated, and 10 subjects rated themselves as moderately intoxicated. This shows that while subjects recognised that they were under the influence of a drug, they had difficulty discriminating whether the drug was alcohol or temazepam.

Average blood alcohol levels by condition were shown to be 0.00 BAC for the placebo condition, O.OO BAC for the temazepam condition, 0.036 BAC for the alcohol condition, and 0.032 BAC for the combined alcohol, temazepam condition.

Performance data were subjected to a two-way ANOVA to test the accuracy of tones counted and the accuracy of the comprehension test in each condition. The 2-way ANOVA showed a trend toward a reduction of comprehension test accuracy by alcohol ($F(1,11) = 3.724$, $MsE = 72.62$, $p = .080$). Similarly temazepam showed a trend toward a reduction of test accuracy ($F(1,11) - 3.553$, $MsE = 233.80$, $p = 0.086$). However alcohol and temazepam in combination produced a significant ($F(1,11) = 10.415$, $MsE = 129.582$) interactive effect upon comprehension test accuracy. As shown in Figure 2 SNKs indicated that alcohol alone, temazepam alone, and combined alcohol and temazepam significantly reduced

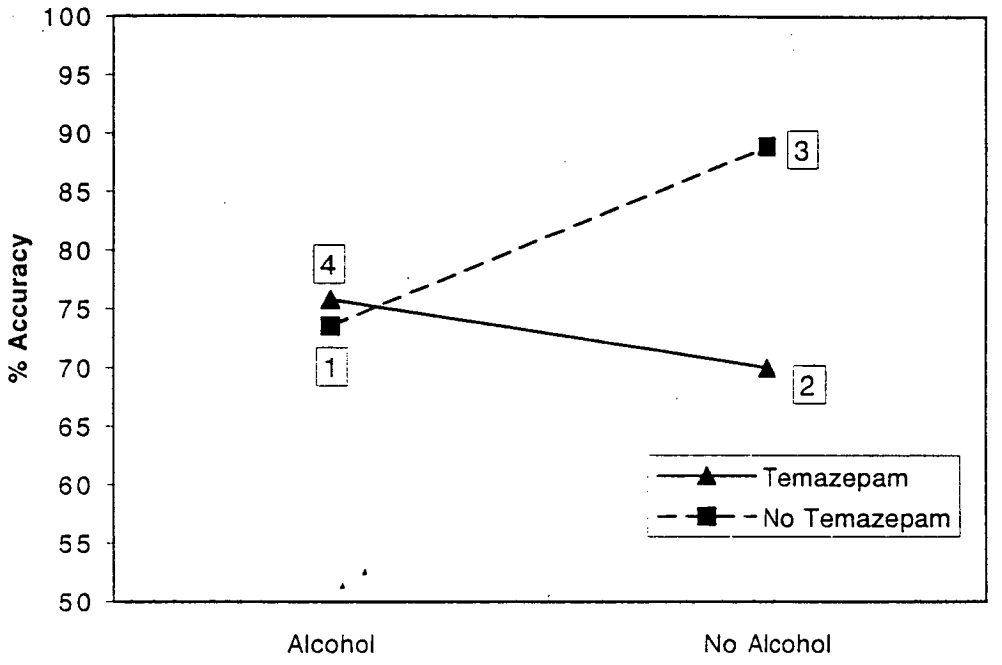

Figure 2. Mean percentage accuracy for comprehension performance under the effects of 1. alcohol, 2. temazepam, 3. placebo, 4. alcohol and temazepam.

comprehension test accuracy compared to the placebo condition. However alcohol in combination with temazepam did not significantly reduce comprehension test performance further than temazepam alone, in fact temazepam and alcohol in combination produced greater test accuracy than temazepam alone.

Grand mean averages for the ERP difference waveforms recorded at each site in each condition are shown in Figure 3. The waveforms show negativity at a latency of about 150 ms. It is not clear that this negativity is MMN, and may include measures of N2b. However this measure is a Negative difference (Nd) and will be referred to as such in the following. At Fz this negativity is clearly identifiable. At Cz and Pz negativity at 150 ms is still observable, although it is greatly reduced compared to Fz. Nds appear to be greater for condition 1 (placebo), slightly reduced for conditions 3 (temazepam) and 4 (alcohol/temazepam), and further reduced in condition 2 (alcohol). Nds at this latency appear to be generally greater in the reading or non-attending conditions, particularly at Cz.

The P3 component of the ERP is clearly identifiable in all conditions at around 300 ms. This component is maximal at Pz in the counting condition and for this condition the effect is reduced at Cz and Fz.

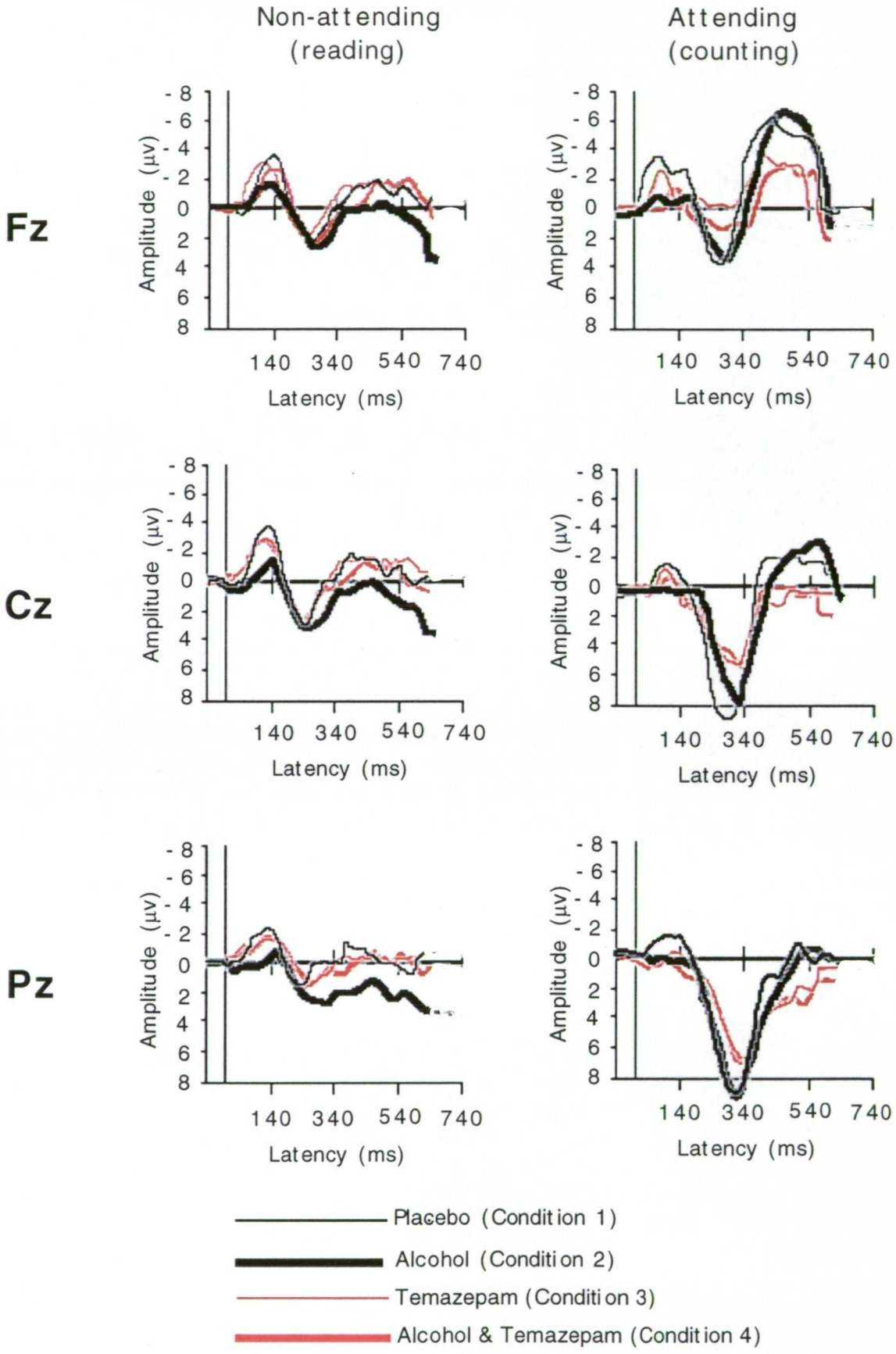

Figure 3. Grand mean difference waveforms at each site in each condition.

P3 amplitude differences appear to be unaffected by condition 2 (alcohol) at any site. However conditions 3 (temazepam) and 4 (alcohol/temazepam) show reduced P3 amplitude differences compared to conditions 1 (placebo) and condition 2 (alcohol) in the counting conditions.

Negative difference (deviant - standard) at 100-300 ms

The four-way ANOVA (temazepam x alcohol x attention x site) performed upon the Nd data showed a significant main effect of attention ($F(1,11) = 11.311$, MsE = 9.040) in which the read (non-attention) condition produced a significantly greater mean Nd than the count attention) condition.

Results also show a significant main effect of site ($F(2,22) = 19.353$, MsE= 3.554, $\varepsilon = 0.92$) in which the mean Nd at Fz was significantly greater than the Nd at both Cz and Pz. The mean Nd at Cz was also significantly greater than that at Pz (SNKs).

Alcohol showed a trend toward a reduction of the mean Nd, $p = 0.097$ ($F(1,11) = 3.289$, MsE = 18.006). Figure 4 demonstrates the significant ($F(2,22) = 7.118$, MsE = 1.600) alcohol x site interaction. SNKs showed that alcohol significantly reduced the Nd at Fz and Cz, but not at Pz. SNKs also show that the Nd in both the alcohol and the no alcohol condition at Fz was significantly greater than those at both Cz and Pz. In the alcohol condition

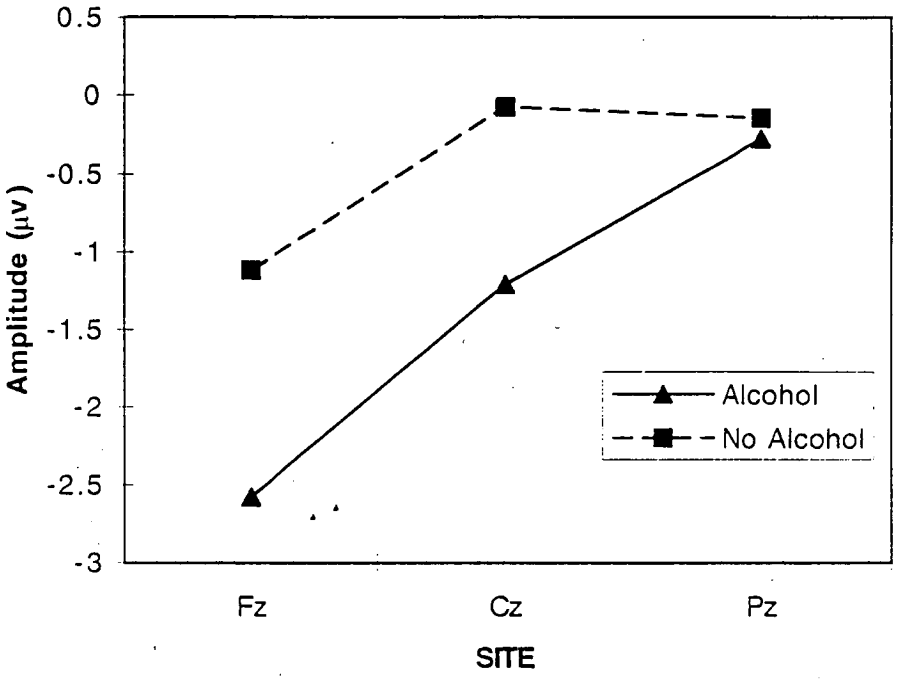

Figure 4. Mean Negative difference at each site for the alcohol and no alcohol conditions.

SNKs showed that the Nd at Fz was significantly greater than those at Cz and Pz.

Figure 5 demonstrates the interaction between task and site which approached significance $p = .065$, ($F(2,22) = 3.096$, $MsE = 5.221$). SNKs showed a significantly reduced Nd in the counting condition at Cz, compared to the reading condition at Cz, and significantly reduced Nd in the counting condition at Pz compared to the reading condition at Pz. Also the counting condition at Fz showed at trend toward a greater mean Nd than the counting condition at Cz and Pz. However in the reading condition greater negativity was not detected at Fz than at Cz or Pz. No other main effects or interactions reached significance.

P3 Component Difference: (Deviant - Standard)

The 4-way (task x alcohol x temazepam x site) ANOVA performed upon the P3 difference data showed a significant ($F(1,11) = 27.403$, $MsE = 61.292$) main effect of task, in which the counting condition produced a significantly greater mean P3 amplitude difference than the reading condition.

The main effect of site was significant ($F(2,22) = 52.745$, $MsE = 4.282$, $\varepsilon = 0.769$). SNKs showed significantly greater mean P3 amplitude differences at Pz than at Cz, and at Cz than at Fz. Figure 6 demonstrates the significant task by site interaction ($F(2,22) = 41.568$,

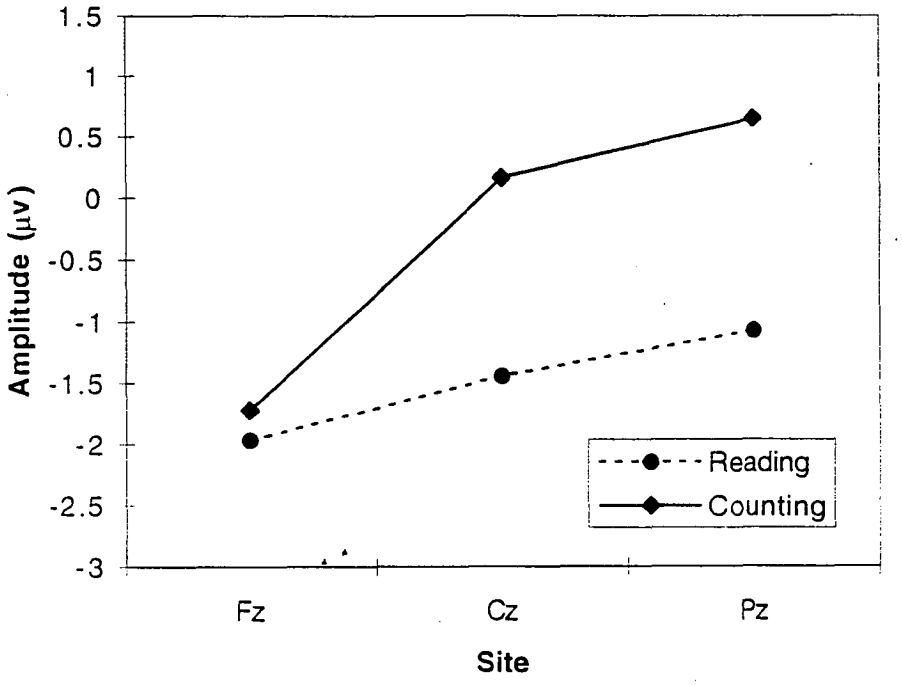

Figure 5. Mean Negative difference for the reading and counting conditions.

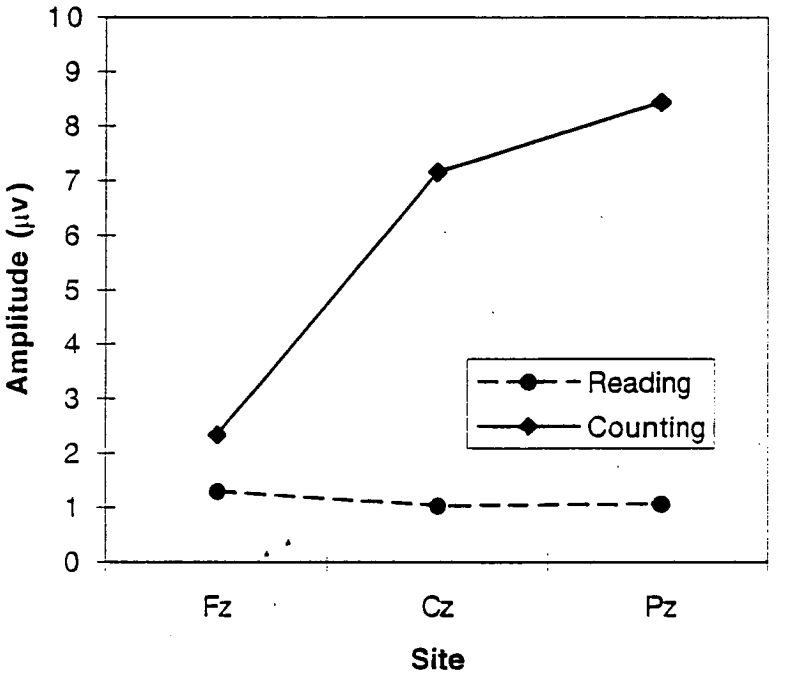

Figure 6. Mean P3 amplitude at each site in the reading and counting conditions.

MsE = 6.483, ε =.363). SNKs showed that the counting condition produced significantly greater mean P3 amplitude differences than reading at Cz and Pz, but not at Fz. Furthermore the mean P3 amplitude differences in the counting condition were significantly greater at Pz than Cz, and at Cz than at Fz.

Figure 7 demonstrates the main effect of temazepam which approached significance p = 0.088, (F(1,11) = 3.504, MsE = 24.391), in which temazepam produced a smaller mean P3 amplitude difference than the no temazepam condition. No other main effects or interactions reached significance.

DISCUSSION

The results of this experiment show that the P3 component of the auditory ERP was enhanced by attention as anticipated (Hillyard & Kutas, 1983). A Nd was found to be evoked at about 130 ms following presentation of a rare stimuli following a sequence of homogenous stimuli. Consistent with other reports of MMN topography (Naatanen, 1988; Woldorff et al., 1991), these results show that negativity was manifested optimally at Fz as expected, however substantial negativity was also detected at Cz and Pz. No effect of attention was recorded at Fz, suggesting that MMN is exogenous. The Nd at Cz and Pz showed an effect of attention in which attention reduced negative amplitude.

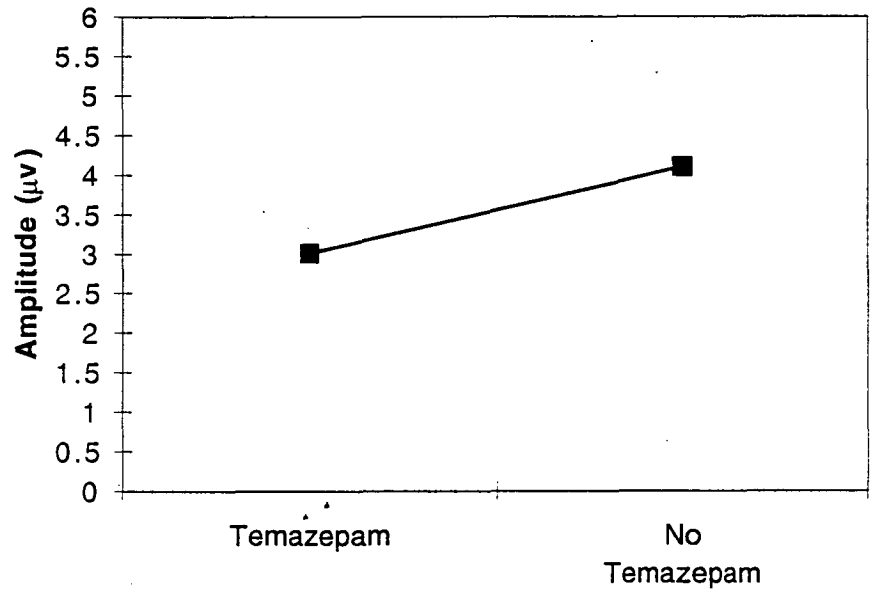

Figure 7. Mean P3 amplitude under the effects of temazepam and no temazepam.

Appraisal of the grand mean difference waveform, and consideration of the site distribution of the Nd suggest that these measures taken at Cz and Pz are a combination of both MMN and N2b, an endogenous component of the ERP.

The performance data show that in the alcohol conditions subjects were channelling attention either to the MMN evoking stimuli or to the text, and fulfilling the attentive or non-attentive conditions as required. However in the temazepam conditions, temazepam significantly reduced the accuracy of the counting task suggesting that the integrity of the attention condition may have been compromised. Temazepam did not significantly reduce the accuracy of the reading task. Further, while temazepam and alcohol individually reduced the accuracy of both tones counted and comprehension, alcohol and temazepam in combination did not interact to further decrease accuracy in either condition. This suggests that alcohol may have enhanced performance by reducing the effect of temazepam upon comprehension.

P3 amplitude was found to be evoked by rare stimuli at about 300 ms post stimulus presentation, primarily at Cz and Pz. The attention condition (counting) produced greater P3 amplitude differences indicating that P3 amplitude was enhanced by attention and confirming the endogeny of this component. The

task by site interaction confirms this strong attentional effect of P3 at Pz. This attentional effect is consistent with the resource allocation model of attention in which the direction of attentional resources to one stimulus reduces the availability of attentional resources to other stimuli (Hillyard & Hansen, 1986). It also suggests that attention modulates cognitive processing (Kahneman & Treisman, 1984). The concentration of attentional resources and processing space upon the attended deviant stimulus had the effect of enhancing the efficiency of processing. Greater P3 amplitude in conditions of attention is an indicator of this.

The Nd analysis showed a greater deviant - standard difference in the reading condition. This initially suggests that the Nd was enhanced in conditions of non-attention, and suppressed in conditions of attention. This can be interpreted as indicating that the sensitivity of neural perception of a deviant stimulus is enhanced when attention is diverted away from the evoking stimulus. However this result is inconsistent with any concept of the Nd as endogenous, but is also inexplicable if the Nd is conceived as exogenous, as differences in the to attentional conditions would be expected to be equal (Naatanen, 1988).

However the attentional effect becomes less incongruous when interpreted in light of the task by site interaction. This interaction demonstrates that the non-

attending (reading) condition recorded a greater Nd at Cz and Pz than did the counting (attending) condition. However the attention/non-attention (count/read) Nds were not significantly different at Fz. While a greater Nd was manifested at Fz in both attended and non-attended conditions, the attention/non-attention difference was not significant at Fz, but only at Cz and Pz, where the non-attentional condition produced significantly greater negativity between 150-250 ms. This Nd recorded at Fz can be interpreted as primarily reflecting MMN and as indicating the absence of an effect of attention upon MMN. However the Nd recorded at Cz and Pz, where the non-attention condition produced significant negativity differences compared to the attention condition, could be interpreted as reflecting the more posteriorly detected N2b. N2b is known to be endogenous and contingent upon the direction of attention toward the evoking stimulus (Naatanen, 1991). In this way the significant Nd elicited in the attention condition is interpreted as reflecting an effect of attention upon N2b at Cz and Pz, and no effect of attention upon MMN at Fz.

A close inspection of the waveforms in Figure 3 supports this supposition. In the attending condition at Fz two negative peaks can be observed at between 100 - 200 ms. The first peak which can be observed is temporally and topographically consistent with the MMN component (Paavilainen, Alho, Reinikainen, Sams, & Naatanen, 1991). The second peak which can be

observed is temporally consistent with the N2b component of the auditory ERP (Naatanen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). The dual negative peaks are not clearly observable at Cz where N2b is usually observed, nor at Pz. It is suggested here that the peaks at Cz and Pz (where the Nd occurred between the attending and non-attending conditions) reflect N2b negativity, or a combination of these two components.

According to this interpretation the Nd recorded at Fz, which is posited to be primarily MMN, was impervious to attenuation by diversion of attention, leading to the conclusion of the exogeny of MMN. This result supports Naatanens' (1988) late selection theory of attention in which perceptual analysis is highly automatic and independent of attentional modulation. The Nd recorded at Cz and Pz, which is posited to be contaminated by the endogenous N2b, was attenuated by the focussing of attention upon the eliciting stimulus. The occurrence of greater negativity to non-attended deviants is inexplicable as this endogenous negativity would be expected to be enhanced in conditions of attention (Naatanen et al., 1993). The reason for this anomaly can be found in the summation of negative amplitude under depressive brain states, and the subtraction of this from normal brain states. Firstly, the statistical comparison conducted within a fully repeated measures design may have led to some contamination of pure conditions by other independent variables. The use

of a relatively small number of subjects (12) might also have exacerbated this effect by increasing the impact of individual subject variation differences, due to latency jitter. The use of a larger subject group is recommended.

The results also show that detection of stimulus deviance was inhibited by alcohol. The alcohol by site interaction showed that alcohol suppressed Nds optimally at Fz and Cz compared to the no alcohol condition. Consistent with this, if alcohol reduces attentional resources then the suppressed Nd measured at Fz which is posited to be principally MMN, suggests that contrary to the above conclusions, MMN is endogenous. However, the fact that alcohol did not affect the endogenous P3 fails to provide support for the effect of low doses of alcohol upon endogenous components only. However as Oscar-Berman (1987) reports, the P3 component is rarely affected by low doses of alcohol. Neither does it confirm the earlier speculation that low doses of alcohol may exert an effect through a reduction of attentional resources in a similar manner to high doses of alcohol (Martin et al., 1993). Because the effect of alcohol on MMN was purported to be as a consequence of reduced attentional resources, and low doses of alcohol have not been shown to exert a reduction on attentional resources, it is concluded that alcohol at this dose has not been a useful tool in contributing to the exogeny or endogeny of MMN. Thus the alcohol manipulations do not dispute the earlier conclusion of the exogeny of MMN.

The effect of alcohol upon MMN may, then, be attributed to generalised CNS depression (Salamy & Williams, 1973). However the lack of P3 attenuation by alcohol suggests that the MMN attenuation is not due purely to CNS depression, unless the effects of CNS depression are alleviated to some degree by the focussing of attention upon endogenous components.

Consistent with previous research (Declerk, 1993) temazepam attenuated the P3 difference waveform at Pz. This indicates that temazepam reduced the amplitude of the P3 in response to the deviant resulting in an amplitude decline toward that of the standard stimulus. That temazepam reduced the amplitude of the endogenous P3 component but not the Nd which, at Fz is interpreted as reflecting the exogenous MMN component, is consistent with reports of sedatives suppressing endogenous components only (Martin et al., 1993). It is also consistent with the performance data recorded in the attention condition, in which temazepam reduced the accuracy of tones counted in the attention condition. However given that these results suggest that the Nd was confounded with N2b at Cz and Pz, an effect of temazepam could have been predicted at negativity between 150-250 ms at these sites due to temazepam affecting the endogenous N2b component. However no Nd waveform was detected at these sites. This suggests that temazepam may affect the P3 component but not

earlier endogenous components such as the N2b. Alternatively confounding of MMN and N2b amplitude may have reduced any difference attributable to temazepam to below significant levels. Further research is necessary to confirm an effect of temazepam upon N2b, and upon endogenous components of the ERP generally.

An alternative interpretation of the effect of temazepam is that it attenuated the amplitude of both standard and deviant components as a consequence of generalised CNS depression. However in this case an effect upon MMN at Fz would also be expected, thus the effect of temazepam does appear to be isolated to later endogenous components.

Temazepam did not affect negativity measured between 100-300 ms at any site. Thus temazepam does not provide any useful information regarding the attentional status of MMN. Consequently the results of this experiment suggest that MMN elicited by pitch deviants is exogenous and impervious to the influence of attentional manipulations. This is inconsistent with the results of Woldorff et al. (1991), who posited that attention affects the efficacy of processing of the MMN component. In this experiment the negative amplitude of MMN as well as the efficiency of the organism's recognition of change does not appear to be enhanced or attenuated according to the direction of attention.

These results support the conclusions of Naatanen and Gaillard (1983) who asserted that MMN is exogenous. Rather than being part of the attentional cognitive process, Naatanen (1985) views MMN as preattentive, subserving the role of attraction and channelling of attention toward unattended environmental change.

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Appendices - contents

Appendix A
Medical history questionnaire

University of Tasmania
Department of Psychology

Medical History Questionnaire

NAME.....

AGE.....PHONE.....

Do you; A. Smoke Cigarettes..... Yes ☐ No ☐
B. Use or have experimented with either drugs or marijuana .....
.....Yes ☐ No ☐

Have you recently lost a lot of weight ?..... Yes ☐ No ☐

Have you ever had any operations ?..... Yes ☐ No ☐

Have you ever been a patient in a Mental hospital?..... Yes ☐ No ☐

Have you ever been a patient in any other hospital ?..... Yes ☐ No ☐

HAVE YOU EVER HAD OR ARE YOU NOW SUFFERING FROM ANY OF THE FOLLOWING;

Tumour, Growth, Cyst, Cancer.....Yes ☐ No ☐

Paralysis (Including Polio)..... Yes ☐ No ☐

Shortness of Breath..... Yes ☐ No ☐

Palpitations or Pounding Heart..... Yes ☐ No ☐

High or Low Blood Pressure..... Yes ☐ No ☐

Heart Disease..... Yes ☐ No ☐

Severe Reactions to Drugs or Injections... Yes ☐ No ☐

Frequent Colds or Nasal Obstructions... Yes ☐ No ☐

Troat troubles..... Yes ☐ No ☐

Fainting Attacks..... Yes ☐ No ☐

Fits or Convulsions..... Yes ☐ No ☐

Appendix A
Medical history questionnaire

Epilepsy.....	Yes ☐	No ☐
Giddiness.....	Yes ☐	No ☐
Severe Headache.....	Yes ☐	No ☐
Migraines.....	Yes ☐	No ☐
Nervous Trouble.....	Yes ☐	No ☐
Severe Depression.....	Yes ☐	No ☐
Mental Illness.....	Yes ☐	No ☐
Attempted Suicide.....	Yes ☐	No ☐
Frequent Indigestion.....	Yes ☐	No ☐
Heartburn.....	Yes ☐	No ☐
Ulcer of the Stomach.....	Yes ☐	No ☐
Ulcer of the Duodenum.....	Yes ☐	No ☐
Gall Bladder Trouble.....	Yes ☐	No ☐
Gall Stones.....	Yes ☐	No ☐
Vomiting Blood.....	Yes ☐	No ☐
Passing Blood Through the Bowels.....	Yes ☐	No ☐
Sugar Diabetes.....	Yes ☐	No ☐
Concussion.....	Yes ☐	No ☐
Severe Head injury.....	Yes ☐	No ☐
Loss of Consciousness.....	Yes ☐	No ☐
Any other Illness or Disability.....	Yes ☐	No ☐

HAVE ANY OF YOUR IMMEDIATE FAMILY OR PEOPLE LIVING WITH YOU:

Been a Heavy Drinker.....	Yes ☐	No ☐
Had Fits.....	Yes ☐	No ☐
Had Epilepsy.....	Yes ☐	No ☐
Had Nervous Illness.....	Yes ☐	No ☐
Had Mental Illness.....	Yes ☐	No ☐

CURRENT MEDICATION

Are you taking any medications at present ? ..... Yes ☐ No ☐

If YES, which Drugs are you taking?

.....

.....

Appendix A
Medical history questionnaire

VISION

Do you wear spectacles?..... Yes ☐ No ☐

Are you Colour Blind?..... Yes ☐ No ☐

Indicate your visual Defect .....

.....

If able, indicate below the exact visual conditions that apply to you;

DISTANT VISION		COLOUR VISION
UNAIDED	CORRECTED TO	
RIGHT 6/	6/	RIGHT:
LEFT 6/	6/	LEFT:

AMSLER FULL FIELD
AMSLER CHART

HEARING

Have you any hearing difficulties? ..... Yes ☐ No ☐
If YES, indicate hearing defects .....

.....

DRINKING HISTORY

On how many days last week did you drink alcohol ?... None ☐
One or Two days ☐
Five or Six Days ☐
Every Day ☐

Do you usually drink..... Never ☐
During the Week ☐
Friday Night ☐
Week Ends Only ☐

When you drink is it Normally..... Light Beer ☐
Beer or Cider ☐
Wine ☐
Mixed spirits ☐
Straight Spirits ☐

Appendix A
Medical history questionnaire

On a day when you drink, how many drinks would you usually have?

- One or Two ☐
- Three to Five ☐
- Five to Eight ☐
- Eight to Twelve ☐
- More than Twelve ☐

How long have you been drinking at this level ?..... Weeks ☐
Months ☐
Years ☐

Do you get drunk?..... Never ☐
Rarely ☐
Once a Month ☐
Once a Week ☐
More Frequently ☐

Does your father get drunk?..... Never ☐
Rarely ☐
Once a Month ☐
Once a Week ☐
More Frequently ☐

Does your Mother get drunk?..... Never ☐
Rarely ☐
Once a Month ☐
Once a Week ☐
More Frequently ☐

Do you have any relatives whom you would consider to be alcoholic?

Yes ☐ No ☐

If YES, How many and what relationship are they to you? .....
.....
.....

Appendix A
Medical history questionnaire

OTHER INFORMATION

How often do you smoke Cigarettes ?..... Never ☐
Less than 10 per day ☐
10 to 20 per day ☐
20 to 40 per day ☐
Over 40 per day ☐

Do you Drive Regularly ? Yes ☐ No ☐
If YES, for how many years have you done so ? .....

.....

Have you ever been involved in a serious road traffic accident ?
Yes ☐ No ☐

If YES, did you sustain any head injuries ? Yes ☐ No ☐

Note:

It is a formal requirement of the Ethics Committee of the University of Tasmania that the information provided on this questionnaire be held under security to comply with confidentiality regulations and to protect your privacy. You can be assured that information will be available only to the principal researcher and not to any other party. The questionnaire will be destroyed following the completion of the project.

Thankyou for your assistance,

Appendix B
Subject consent form

THE UNIVERSITY OF TASMANIA

PSYCHOLOGY DEPARTMENT

Information for participation in studies in the Electrophysiological Research Laboratory.

NAME.....

PHONE.....

The research carried out in the Electroencephalographic Research Laboratory includes a number of continuing research projects. Our studies are concerned with understanding more about the nature of cognitive processes, brain activity and a number of related phenomena. The success of our research depends upon the assistance of volunteers like yourself, and we are extremely grateful for your participation. Please sign and date this form after reading the following section;

Today I am volunteering to participate in a research study that involves the presentation of auditory stimuli. I understand that the electrical activity of my brain will be measured and that I will be given either a placebo or a 10 mg dose of Temazepam, a placebo and alcohol to the level of 0.04% blood alcohol, or a 10 mg dose of Temazepam and alcohol to the level of 0.04% blood alcohol, or two placebos. I also understand that I should not drive a car or drink any alcohol for 24 hours following the study. My participation will also involve discussing my experience of and reaction to the study. I also understand that I am free to discontinue my participation at any time.

SIGNATURE..... DATE.....

I have explained this project and the implications of participation in it to this volunteer and I believe that the consent is informed and that she understands the implications of participation.

Researcher signature..... Date.....

Appendix C

Subject Instructions for Conditions 1 & 3

Thankyou for participating in this experiment. In a moment I want you to start reading the text. Try to reduce body movement to a minimum and keep your eyes as still as possible, not moving them up or down the page and blinking as little as possible. During the experiment you will hear tones coming through the headphones, please ignore them as much as you can and concentrate upon what you are reading. I will give you a short comprehension test at the end to assess your concentration. Do you have any questions?

Subject Instructions for Conditions 2 & 4

Thankyou for participating in this experiment. In a moment you will hear some tones coming through the headphones. Most of the tones will be standard tones, sounding exactly the same, but occasionally you will hear tones of a different pitch. I want you to listen carefully to the tones and count the odd tones, so that you can report the total number at the end of the experiment. Try to reduce body movement to a minimum and keep your eyes still, blinking as little as possible. Do you have any questions?

Appendix D
Comprehension tests

The woman in the story was named
- Conchetta
- Rosa
- Maria
- Juanita
- Anita

What did she carry over her shoulder as she walked down the road?
- jacal
- food basket
- baby
- fowls
- rebozo

The woman in the story was
- Jewish
- Catholic
- Anglican
- Buddhist

What did she crave on the bridge?
- nuts
- fruit
- honey
- chicken

The American archaeologist was called
- Givens
- Villegas
- Lutas
- Saul

The couple in the story got married in a
- garden
- behind the manse
- behind the church
- church

One day she came home to find her
- coins gone
- jacal gone
- beehives gone
- chickens gone
- rebozo gone

After her husband and mistress left she cared for
- bees
- fowls
- garden
- church
- children

Juan went home to his wife to
- apologise to her
- hide her away
- beat her
- make his mistress jealous

Lupe said that the retreating footfalls sounded
-heavy
- light
- splashing in the stream
- like an evil spirit

How did Juan feel when his mistress died?
- relieved
- bitter
- betrayed
- frustrated

After it's mother died the baby was fed
- goats milk
- human milk
- spring water
- cows milk

Appendix D
Comprehension tests

The masters first son
- died
- went away to school
- went abroad
- went missing at the river

When the little master went missing everyone thought
- Padma had swallowed the child
- Raicharan had murdered the child
- the child had run away
- the child had drowned

At first Raicharan thought that his son was
- a reincarnation of the little master
- illegitimate
- beautiful
- an usurper

The other children called Raicharan's son
- Phailna
- spoiled
- your lordship
- little Raicharan

Phailna loved his father with
- a kind of condescension
- a pure and earnest dedication
- shame born out of pride
- reservations

Raicharan's employer found fault with him because
- he was old
- he was physically weak
- he wanted more money
- he was stealing to support his son

Raicharan went home
- because he lost his job
- to see his old master
- to find work
- to retire

When Anukul's wife saw Phailna she
- stared
- was angry
- asked for proof
- took him upon her lap

Raicharan asked for forgiveness saying the fault lay with
- the villagers
- Anukul
- God
- Phailna's fate

Anukul considered himself
- a modest man
- a just man
- an educated man
- an evil man

How did Phailna feel initially when he realised his birthright
- distressed
- angry
- forgiving
- generous

When Anukul sent money it was returned because
- Raicharan was dead
- Raicharan was travelling
- Raicharan was too proud to take it
- No one by the name of Raicharan was there

Appendix D
Comprehension tests

Charles wanted Mr Schaeffer to have
- his sister's phone number
- his brother-in-law's address
- his brother's phone number
- his sister-in-law's address

Paris was
- empty
- sunny
- disappointing
- strange and portentous

Claude ran up a bill of
- 300 franc
- 3,000 francs
- 30,000 francs
- 300,000 francs

Charlie had never
- been to America
- been to a cheap hotel
- been to Ireland
- been to a cheap restaurant

Charlie was
- 29
- 35
- 36
- 42

The little girl was
- 6
- 7
- 8
- 9

Charlie called her
- his little girl
- my old pie
- my doll
- angel

Her real name was
- Marion
- Lorraine
- Helen
- Honoria

Charlie recalled giving the orchestra
- ten franc notes
- fifty franc notes
- hundred franc notes
- thousand franc notes

Charlies wife was buried in
- Montmartre
- Czechoslovakia
- Vermont
- Griffiths

Charlie really came to Paris
- to take custody of his daughter
- business
- give up drinking
- visit Honoria

Charlie believed that
- Helen hadn't wanted him to be alone
- Honoria needed her father
- he was incorrigible drunk
- he had nothing to live for except Honoria

Appendix D
Comprehension tests

As he wrote Vanka looked fearfully
- at his master's cupboard
- at the dark icon
- at the door and windows
- at his masters tools

Vanka's grandfather was
- a night watchman
- a cobbler
- a clerk
- a servant

The dogs were named
- Brownie and Elle
- Brownie and Eel
- Bateman and Eel
- Bateman and Elle

The grandfather gave the dogs
- peasant's chickens
- dog food
- scraps from the kitchen
- snuff

Vanka was forced to sleep
- on the floor
- in the babies room
- in the passageway
- inside the door

Vanka said his life
- was worse than a dog's life
- was lonely
- was empty
- was not worth living

The Happy Prince's eyes were
- green beryls
- emeralds
- sapphires
- rubies

The swallow's friend's had gone
- south
- Sans Souici
- Turkey
- Egypt

The swallow was afraid that the reed
- was a coquette
- had too many relations
- didn't have enough money
- would not go away with him

The ill child wanted
- passionfruit
- soup
- oranges
- water

Children laughed because they had
- bread
- gold leaves
- money
- health

When the heart wouldn't melt the workmen took it to
- the scrap heap
- the church
- the furnace
- god

Appendix E

Subject % blood alcohol content during experiment

	Condition 1	Condition 2	Condition 3	Condition 4
1	0.00	0.03	0.00	0.035
2	0.00	0.05	0.00	0.035
3	0.00	0.025	0.00	0.02
4	0.00	0.035	0.00	0.045
5	0.00	0.035	0.00	0.03
6	0.00	0.035	0.00	0.04
7	0.00	0.035	0.00	0.035
8	0.00	0.05	0.00	0.02
9	0.00	0.03	0.00	0.03
10	0.00	0.04	0.00	0.04
11	0.00	0.04	0.0	0.03
12	0.00	0.03	0.00	0.03

Appendix F

Subjective Intoxication Rating

0 Totally unaffected by alcohol, sober.

1. Slightly affected by alcohol, still capable of driving.

2. Affected by alcohol, dubious whether or not I would drive a car.

3. Intoxcated, probably unable to drive.

4. Very intoxicated, definitely unable to drive

Appendix F

Subjective Sedation Rating

0 Totally unaffected by Temazepam, ie., not sedated.

1 Slightly sedated, still capable of driving.

2 Moderately sedated, dubious whether or not I would drive a car.

3 Very sedated, probably unable to drive.

4 Definitely unable to drive.

1 5

Normal and alert

Extremely sedate, Almost asleep

Appendix G
Raw ERP data

	1 N2_C1RFZ	2 N2_C1RCZ	3 N2_C1RPZ	4 N2_C3RFZ	5 N2_C3RCZ	6 N2_C3RPZ	7 N2_C2RFZ	8 N2_C2RCZ	9 N2_C2RPZ
1	-1.300	.400	-2.200	1.200	.900	.900	-3.700	-3.800	-2.100
2	-8.100	-7.400	-3.000	-2.900	-2.900	2.000	-4.600	-4.000	-2.100
3	-3.000	1.300	-2.200	-2.100	-1.400	-.400	5.800	7.500	4.500
4	-4.900	-4.200	-3.200	-5.200	-2.900	-.700	-3.900	-1.700	-1.200
5	-2.300	-2.600	-1.100	2.500	1.700	1.300	1.900	1.800	-.400
6	.300	-1.300	-2.400	-3.100	-2.800	0.000	-3.300	-3.400	-1.800
7	-5.000	-4.100	-1.500	-1.800	-2.200	-1.300	1.700	4.300	2.000
8	-3.700	-1.900	-3.200	-3.200	-2.100	-.600	-2.200	-2.200	-3.600
9	-2.000	-2.800	-1.300	.800	.900	1.300	-.300	0.000	1.600
10	-1.900	-2.200	-1.700	-1.300	-2.200	-1.900	.500	-.500	-1.600
11	-.600	4.100	.100	-5.300	-5.200	-1.900	-2.600	-2.000	-.600
12	-2.500	-2.300	-2.600	-5.700	-4.400	-3.500	-1.800	-1.500	-1.600

	10 N2_C4RFZ	11 N2_C4RCZ	12 N2_C4RPZ	13 N2_C1CFZ	14 N2_C1CCZ	15 N2_C1CPZ	16 N2_C3CFZ	17 N2_C3CCZ	18 N2_C3CPZ
1	-2.000	-2.100	-2.700	-4.800	1.100	3.700	-1.400	2.100	2.500
2	-4.500	-4.200	-2.100	-2.700	-1.500	-1.400	-2.600	-1.600	1.500
3	-1.400	-1.700	-2.800	2.400	.900	4.700	-2.600	1.100	1.300
4	-2.600	-4.400	-3.800	-1.900	-5.000	-4.400	-.100	-2.300	-.800
5	2.100	2.900	0.000	-3.700	2.800	5.300	-2.100	3.900	1.400
6	.200	-1.800	-1.100	-.700	.700	1.500	-3.400	-3.200	-2.100
7	-1.600	-1.900	0.000	-6.600	-2.300	-2.100	-3.300	-2.100	1.300
8	-2.200	-.900	-.300	-4.000	1.700	-1.200	-1.500	.700	.200
9	-6.000	-3.900	-3.100	-9.700	-6.400	-5.800	-1.300	-.600	2.800
10	.400	.200	-.300	-.300	.700	2.100	-6.300	-2.900	-1.900
11	-3.600	-1.200	.600	.700	2.200	3.900	-.100	3.500	5.400
12	-1.000	-.500	0.000	-1.100	-2.200	-1.600	-5.500	-4.000	-.800

	19 N2_C2CFZ	20 N2_C2CCZ	21 N2_C2CPZ	22 N2_C4CFZ	23 N2_C4CCZ	24 N2_C4CPZ	25 P3_C1CFZ	26 P3_C1CCZ	27 P3_C1CPZ
1	-6.000	.500	-.600	-1.700	-2.500	-.400	6.100	10.900	10.600
2	.900	-.100	.600	3.000	2.100	-1.000	3.600	11.300	8.800
3	3.700	1.200	1.400	-1.300	.700	1.400	1.400	4.000	4.000
4	2.300	-1.100	-1.300	3.600	2.000	1.500	5.000	10.200	11.200
5	0.000	4.900	-.800	-.600	3.300	3.400	2.800	11.100	11.900
6	-3.500	-.800	-1.200	.100	.700	-.100	2.400	6.500	8.200
7	7.600	7.700	7.000	-4.100	-1.300	-2.100	-.800	5.000	2.000
8	-2.800	1.100	3.100	-3.300	2.100	-1.100	-1.800	6.300	11.400
9	-6.000	-3.100	-3.400	2.200	6.400	3.700	4.400	11.500	10.900
10	-4.600	-2.400	-1.200	-2.800	-2.000	-1.500	2.100	6.100	8.700
11	-2.700	-2.000	.300	-.300	2.600	2.200	6.300	8.400	10.900
12	-3.700	0.000	1.200	-.300	.400	.200	1.600	4.900	5.000

	28 P3_C3CFZ	29 P3_C3CCZ	30 P3_C3CPZ	31 P3_C2CFZ	32 P3C2CCZ	33 P3_C2CPZ	34 P3_C4CFZ	35 P3_C4CCZ	36 P3_C4CPZ
1	.100	6.100	7.100	2.900	8.500	9.200	-7.600	-2.300	1.800
2	3.000	8.600	6.500	9.400	19.100	18.400	2.400	1.700	-1.900
3	.900	4.500	4.800	3.200	6.800	9.300	3.700	9.700	10.100
4	9.200	19.000	24.100	11.700	20.700	22.200	13.400	14.100	17.400
5	-2.900	4.800	5.000	1.700	6.700	6.900	-1.400	3.700	6.000
6	4.100	11.000	10.700	.800	6.800	10.400	1.600	6.500	6.200
7	-2.300	2.800	2.800	6.800	0.000	6.700	-1.200	3.100	4.600
8	-2.700	.300	2.200	-1.100	4.500	9.500	-2.400	8.900	13.100
9	-2.200	-2.700	-.600	.100	5.300	6.100	4.000	8.200	9.700
10	-4.300	2.700	5.200	2.100	4.300	5.000	2.300	5.100	7.200
11	7.300	15.400	18.100	11.300	13.200	13.700	7.300	12.200	13.300
12	-1.400	2.200	3.300	-1.400	3.200	5.300	0.000	1.700	1.200

	37 P3_C1RFZ	38 P3_C1RCZ	39 P3_C1RPZ	40 P3_C3RFZ	41 P3_C3RCZ	42 P3_C3RPZ	43 P3_C2RFZ	44 P3_C2RCZ	45 P3_C2RPZ
1	-2.300	-.600	0.000	1.300	2.700	4.200	-.500	-1.800	-4.300
2	1.200	5.300	5.200	.400	-.300	2.500	2.000	3.400	2.300
3	3.000	-.600	-1.200	3.600	3.400	1.300	6.400	8.200	7.400
4	3.400	4.300	-2.100	1.100	-4.000	-1.200	6.200	-3.800	-3.500
5	1.000	-2.700	-.500	5.100	6.400	6.100	2.800	2.300	4.500
6	.800	-.100	-.900	1.500	.800	1.400	.900	.500	1.500
7	-.400	-.100	.800	0.000	-.300	-2.000	2.700	3.500	5.300
8	-4.400	-4.200	-2.200	-2.900	-2.200	-2.600	-1.300	-1.800	-1.100
9	5.700	4.900	4.000	1.300	1.000	1.200	4.800	4.200	4.700
10	-.200	-2.100	-.400	-.300	-1.700	-1.600	.600	.200	.900
11	1.600	5.100	2.400	2.100	3.000	2.700	4.700	.200	-.800
12	.900	1.100	1.200	-3.600	-2.400	-1.300	.100	-.900	-.500

	46 P3_C4RFZ	47 P3_C4RCZ	48 P3_C4RPZ	49 VAR49	50 VAR50	51 VAR51	52 VAR52	53 VAR53	54 VAR54
1	-2.500	-1.600	-.900						
2	4.900	6.800	5.400						
3	-1.900	-2.100	-3.600						
4	11.000	9.700	6.100						
5	2.100	2.600	2.700						
6	1.100	0.000	1.700						
7	-2.900	-2.700	0.000						
8	-3.200	-1.100	-.100						
9	2.400	2.700	2.600						
10	.300	.300	.700						
11	3.800	5.000	3.600						
12	-1.800	-1.300	-.500						

Appendix H
Statistical tests for ERP data

Four way ANOVA- task (2) x alcohol (2) x drug (2) x site (3) Nd

STAT. GENERAL MANOVA	Summary of all Effects; design: (roseanne.sta) 1-TASK/R/C, 2-ALC/N/Y, 3-TEM/N/Y, 4-SITEFCP					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1*	102.2450*	11*	9.03955*	11.31086*	.006328*
2	1	59.2235	11	18.00559	3.28917	.097084
3	1	3.4672	11	20.87449	.16610	.691422
4	2*	68.7801*	22*	3.55389*	19.35349*	.000014*
12	1	1.3339	11	10.27934	.12976	.725498
13	1	4.2535	11	19.35650	.21974	.648388
23	1	7.4756	11	20.98647	.35621	.562702
14	2	16.1679	22	5.22144	3.09645	.065330
24	2*	11.3901*	22*	1.60010*	7.11839*	.004131*
34	2	1.5376	22	.90298	1.70285	.205308
123	1	18.1001	11	9.41014	1.92347	.192935
124	2	1.4156	22	.73953	1.91412	.171240
134	2	1.3793	22	1.86972	.73771	.489671
234	2	1.5072	22	2.13074	.70737	.503811
1234	2	.1226	22	1.90366	.06442	.937785

Mean Nd amplitude in each condition

STAT. GENERAL MANOVA				Means (roseanne.sta) Rao R (2,10)=.05; p<.9502
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP	Depend. Var.1
1	1	1	1	-2.91667
1	1	1	2	-1.91667
1	1	1	3	-2.02500
1	1	2	1	-2.17500
1	1	2	2	-1.88333
1	1	2	3	-.40000
1	2	1	1	-1.04167
1	2	1	2	-.45833
1	2	1	3	-.57500
1	2	2	1	-1.75833
1	2	2	2	-1.55833
1	2	2	3	-1.30000
2	1	1	1	-2.70000
2	1	1	2	-.60833
2	1	1	3	.39167
2	1	2	1	-2.51667
2	1	2	2	-.45000
2	1	2	3	.90000
2	2	1	1	-1.23333
2	2	1	2	.48333
2	2	1	3	.42500
2	2	2	1	-.45833
2	2	2	2	1.20833
2	2	2	3	.85000

Appendix H
Statistical tests for ERP data

Student Newman-Keuls for the main effect of site - Nd

STAT. GENERAL MANOVA					Newman-Keuls test; Var.1 (roseanne.sta) Probabilities for Post Hoc Tests MAIN EFFECT: SITEFCP		
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP		(1) -1.85000	(2) -.647917	(3) -.216667
....	....	....	1	(1)		.000359 *	.000145 *
....	....	....	2	(2)	.000359 *		.127407
....	....	....	3	(3)	.000145 *	.127407	

Student Newman-Keuls for the alcohol x site interaction - Nd

STAT. GENERAL MANOVA					Newman-Keuls test; Var.1 (roseanne.sta) Probabilities for Post Hoc Tests INTERACTION: 2 x 4			
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP		(1) -2.57708	(2) -1.21458	(3) -.283333	(4) -.133292
....	1	....	1	(1)		.000172*	.000167*	.000161*
....	1	....	2	(2)	.000172*		.004393*	.726094
....	1	....	3	(3)	.000167*	.004393*		.003802*
....	2	....	1	(4)	.000161*	.726094	.003802*	
....	2	....	2	(5)	.000144*	.002066*	.717433	.003003*
....	2	....	3	(6)	.000124*	.002457*	.610862	.003024*

STAT. GENERAL MANOVA					Newman-Keuls test; Var.1 (roseanne.sta) Probabilities for Post Hoc Tests INTERACTION: 2 x 4	
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP		(5) -.081250	(6) -.150000
....	1	....	1	(1)	.000144*	.000124*
....	1	....	2	(2)	.002066*	.002457*
....	1	....	3	(3)	.717433	.610862
....	2	....	1	(4)	.003003*	.003024*
....	2	....	2	(5)		.792634
....	2	....	3	(6)	.792634	

Appendix H
Statistical tests for ERP data

Four way ANOVA - task (2) x alcohol (2) x drug (2) x site (3) - P3

STAT. GENERAL MANOVA	Summary of all Effects; design: (roseanne.sta) 1-TASK/R/C, 2-ALC/N/Y, 3-TEM/N/Y, 4-SITEFCP					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1*	1679.584*	11*	61.29193*	27.40302*	.000279*
2	1	36.623	11	22.53208	1.62535	.228618
3	1	85.478	11	24.39100	3.50448	.088013
4	2*	225.844*	22*	4.28185*	52.74450*	.000000*
12	1	.195	11	3.63031	.05380	.820836
13	1	62.627	11	27.16837	2.30513	.157151
23	1	4.278	11	22.42342	.19077	.670723
14	2*	269.484*	22*	6.48297*	41.56798*	.000000*
24	2	3.186	22	3.17411	1.00390	.382624
34	2	1.551	22	3.23923	.47880	.625834
123	1	.813	11	56.67690	.01434	.906837
124	2	1.163	22	1.85726	.62598	.543996
134	2	1.305	22	2.11729	.61627	.549016
234	2	1.918	22	3.05711	.62753	.543196
1234	2	3.119	22	4.59806	.67830	.517779

Mean P3 amplitude in each condition

STAT. GENERAL MANOVA				Means (roseanne.sta) Rao R (2,10)=.61; p<.4711
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP	Depend. Var.1
1	1	1	1	.85833
1	1	1	2	.90000
1	1	1	3	.52500
1	1	2	1	.80000
1	1	2	2	.53333
1	1	2	3	.89167
1	2	1	1	3.45000
1	2	1	2	1.18333
1	2	1	3	1.35833
1	2	2	1	1.10833
1	2	2	2	1.52500
1	2	2	3	1.47500
2	1	1	1	2.75833
2	1	1	2	8.01667
2	1	1	3	8.63333
2	1	2	1	.73333
2	1	2	2	6.22500
2	1	2	3	7.43333
2	2	1	1	3.95833
2	2	1	2	8.25833
2	2	1	3	10.22500
2	2	2	1	1.88333
2	2	2	2	6.05000
2	2	2	3	7.39167

Appendix H
Statistical tests for ERP data

Student Newman-Keuls for the main effect of site - P3

STAT. GENERAL MANOVA				Newman-Keuls test; Var.1 (roseanne.sta) Probabilities for Post Hoc Tests MAIN EFFECT: SITEFCP		
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP	{1} 1.818750	{2} 4.086458	{3} 4.741667
....	....	....	1 {1}		.000144 *	.000136 *
....	....	....	2 {2}	.000144 *		.039245 *
....	....	....	3 {3}	.000136 *	.039245 *	

Student Newman-Keuls for the task x site interaction - P3

STAT. GENERAL MANOVA				Newman-Keuls test; Var.1 (roseanne.sta) Probabilities for Post Hoc Tests INTERACTION: 1 x 4			
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP	{1} 1.304167	{2} 1.035417	{3} 1.062500	{4} 2.333333
1	....	....	1 {1}		.863931	.646656	.060463
1	....	....	2 {2}	.863931		.959036	.088301
1	....	....	3 {3}	.646656	.959036		.057488
2	....	....	1 {4}	.060463	.088301	.057488	
2	....	....	2 {5}	.000136*	.000124*	.000167*	.000144*
2	....	....	3 {6}	.000167*	.000144*	.000124*	.000136*

STAT. GENERAL MANOVA				Newman-Keuls test; Var.1 (roseanne.sta) Probabilities for Post Hoc Tests INTERACTION: 1 x 4	
TASK/R/C	ALC/N/Y	TEM/N/Y	SITEFCP	{5} 7.137500	{6} 8.420834
1	....	....	1 {1}	.000136*	.000167*
1	....	....	2 {2}	.000124*	.000144*
1	....	....	3 {3}	.000167*	.000124*
2	....	....	1 {4}	.000144*	.000136*
2	....	....	2 {5}		.021921*
2	....	....	3 {6}	.021921*	

Appendix I

Percentage accuracy for comprehension test for each subject

	Condition 1	Condition 2	Condition 3	Condition 4
1	91.67	58.34	58.34	91.67
2	83.34	91.67	83.34	66.67
3	93.75	83.34	66.67	91.67
4	83.34	66.67	75	75
5	91.67	75	66.67	50
6	100	91.67	58.34	58.34
7	50	33.34	58.34	66.67
8	100	83.34	85.71	83.34
9	91.67	83.34	50	83.34
10	100	66.67	75	75
11	91.67	75	91.67	91.67
12	88.83	73.49	69.92	75.76

Appendix I

Percentage accuracy of tones counted for each subject

	Condition 1	Condition 2	Condition 3	Condition 4
1	100	100	93.5	100
2	100	100.5	99.5	99.5
3	99	94	77	83
4	100	99.5	80	99
5	99.5	82	109.5	82
6	106	107	107	108
7	100	100	95	25
8	101	99.5	102	103
9	100	100	50	100
10	100	99	70.5	78.5
11	100	100	99.5	108.5
12	100.5	90.1	89.5	89.5

Appendix J
Statistical tests for performance data

Two way ANOVA - alcohol (2) x drug (2) for % accuracy of comprehension test

STAT. GENERAL MANOVA	Summary of all Effects; design: (rosebper.sta) 1-ALCY/N, 2-TEMY/N					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	20.150	11	226.5093	.088960	.771263
2	1*	1087.755*	11*	202.8007*	5.363667*	.040868*
12	1	29.610	11	186.5466	.158728	.697954

Mean % accuracy for tones counted for the effects of temazepam

STAT. GENERAL MANOVA	Means (rosebper.sta) F(1,11)=5.36; p<.0409
ALCY/N TEMY/N	Depend. Var.1
[illegible]	[illegible]

Appendix J
Statistical tests for performance data

Two way ANOVA - alcohol (2) x drug (2) for % accuracy of tones counted

STAT. GENERAL MANOVA	Summary of all Effects; design: (rosebper.sta) 1-ALCN/Y, 2-TEMN/Y					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	270.4455	11	72.6240	3.72418	.079812
2	1	930.6683	11	233.7963	3.85296	.076117
12	1*	1346.201*	11*	129.2582*	10.41482*	.008055*

Mean % accuracy for tones counted for effects of drug

STAT. GENERAL MANOVA		Means (rosebper.sta) F(1,11)=3.85; p<.0761
ALCN/Y	TEMN/Y	Depend. Var.1
....	1	81.13673
....	2	72.62875

Student Newman-Keuls for the alcohol x drug interaction upon % accuracy of tones counted

STAT. GENERAL MANOVA			Newman-Keuls test; Var... Probabilities for Post Hoc Tests INTERACTION: 1 x 2			
ALCN/Y	TEMN/Y		(1) 88.82833	(2) 69.91666	(3) 73.48917	(4) 75.76083
1	1	(1)		.008607*	.017854*	.016968*
1	2	(2)	.008607*		.457879	.445558
2	1	(3)	.017854*	.457879		.624313
2	2	(4)	.016968*	.445558	.624313	

Mean % accuracy for tones counted for the alcohol x drug interaction

STAT. GENERAL MANOVA		Means (rosebper.sta) F(1,11)=10.41; p<.0081
ALCN/Y	TEMN/Y	Depend. Var.1
1	1	88.82833
1	2	69.91666
2	1	73.48917
2	2	75.76083

Appendix K

Subjective Sedation ratings for each subject

	Condition 1	Condition 2	Condition 3	Condition 4
1	0	0	3	2
2	1	0	1	1
3	0	1	0	1
4	0	1	1	2
5	0	1	1	1
6	0	1	1	1
7	0	2	1	1
8	0	1	2	2
9	0	3	3	3
10	1	1	1	2
11	0	0	2	3
12	0	1	1	0

Appendix K

Subjective Intoxication ratings for each subject

	Condition 1	Condition 2	Condition 3	Condition 4
1	0	2	0	4
2	0	0	0	2
3	0	1	0	2
4	0	0	0	0
5	0	2	0	1
6	0	1	1	1
7	1	2	0	0
8	0	1	1	2
9	0	3	3	2
10	0	1	0	3
11	0	2	2	3
12	0	2	0	2