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The chronometrics of cortical excitation as explored with auditory probes

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Abstract In a series of studies we examined sensory evoked potentials to stimuli presented while subjects performed a primary task. The primary tasks were designed to induce changes in slow cortical potentials (SCP) such as P300, contingent negative variation (CNV), and postimperative negative variation (PINV). Brief auditory stimuli were presented before, during or after the primary task. The interactions between the two types of event-related potentials, SCP and the probe-evoked N1/P2, served to further explore the nature of SCP, particularly in its relation to excitability in cortical neuronal networks. The functional state indicated by SCP was also probed in patients with a chronic schizophrenic disorder, who are known to exhibit deviant SCP. Increased amplitudes of the probe-evoked vertex potential (N1/P2) and faster motor responses to probes during the CNV, and reduced N1/P2-amplitudes and delayed motor responses during positive waves (P300) support the hypothesis that anticipatory cortical negativity indicates excitation in cortical neuronal networks while positive-going waves may indicate widespread cortical suppression (with focused islands of cortical excitability). Increased amplitudes of the N1/P2 during the CNV but not during the PINV suggest a different functional significance of these two negative-going slow waves. Although schizophrenic patients displayed different amplitudes and scalp distribution, particularly of the PINV, suggesting a deviant spatio-temporal regulation of cortical excitability, the functional relation between SCP and probe-related activity was similar in schizophrenic patients and control subjects.

Introduction and theoretical background

Slow cortical potentials (SCP) can be measured from the surface of the scalp when tens of thousands of cortical pyramidal cells are synchronously depolarized. The excitatory postsynaptic potentials that depolarize the apical dendritic trees of cortical pyramidal cells result in surface-negative potentials (Caspers, Speckmann, & Lehmenkühler, 1984, 1987; Speckmann, Caspers, & Elger, 1984). A negative potential over larger cortical surfaces will generally result in a surface negativity also visible on the scalp. A state characterized by surface-negative SCPs might therefore generally indicate a state of higher neural excitability or activation of the underlying neuronal networks (Elbert, 1993; Elbert & Rockstroh, 1987; Rösler, 1991). When an afferent volley reaches such an excitable cortical region, cell assemblies therein should ignite more easily compared to conditions when the same input reaches the network during states of reduced depolarization. The latter states would be characterized by relative surface positivity. Consequently, facilitated responding to an afferent input is to be expected, i. e., the evoked potential should be larger in amplitude when it is elicited during a surface negative shift in regions where the stimulus is processed, but smaller during positive potentials. We have developed a model of regulation of cortical excitability (Elbert, 1993; Elbert & Rockstroh, 1987; Rockstroh, Elbert, Canavan, Lutzenberger, & Birbaumer, 1989; Birbaumer, Elbert, Canavan, & Rockstroh, 1990) suggesting that the extent of depolarization in the various cortical regions must be controlled in order to regulate the spread of activation. At any given instant in time, gross levels of cortical activation are measured through descending information to the striatum and the basal ganglia which in

turn control cortical excitability through the thalamus, reducing excitation before the sum of ignited cell assemblies tends to explode in a chain reaction, and attenuating excitability before the spread of patterns of activation will cease (Elbert, 1993; Elbert & Rockstroh, 1987). Thus, cortical depolarization will not only indicate the actual loci of processing but also regions in which the thresholds for firing are reduced as they are expected to become involved in the next moments. CNV (contingent negative variation), BP (Bereitschaftspotential) or SPN (stimulus-preceding negativity) are typical examples of such anticipatory negativities, indicating lowered firing thresholds in distinct cortical regions. Rockstroh et al. (1989) have concluded that, as a consequence of this mechanism, negativity indicates response facilitation (experimental evidence provided, for instance, by Rockstroh, Elbert, Lutzenberger, & Birbaumer, 1982) but also a greater likelihood for false alarms (Lutzenberger, Birbaumer, Elbert, & Rockstroh, 1979). We have adopted the Hebbian view of cell assemblies, i. e., mutually exciting connections among neural elements pertaining to a certain concept. If the neural representation of a concept is activated, the number of active elements in the brain and cortex will increase. According to the concept of threshold control (Braitenberg, & Schüz, 1991) thresholds will be immediately raised and elements that were previously active will be silent a moment later. The neural elements representing the concept are likely to survive, because (a) afferent input is fed into the cell assembly, and (b) the reciprocally excitatory connections within the cell assembly resist the shut down of the cell assembly. Only the activity in elements without current input will be terminated. We would consider the focusing of attention, i. e., the focusing on individual concepts, to be a consequence of this process. In this way, threshold control may constitute a physiological mechanism underlying attention.

Approaches to confirming the neurophysiological meaning of these SCP include, for instance, cross correlation of surface and intracranial recordings (e. g., Speckmann et al., 1984), or the pharmacological manipulation of SCP (Rockstroh et al., 1989, Rockstroh, 1990). The psychophysiological function of SCP can be uncovered by examining the surface distribution of the SCP in dependence on tasks that are known to activate specific brain areas (e. g., Rösler, Heil, & Glowalla, 1993; Rösler, Heil, & Hennighausen, 1995 b).

In the present paper, we discuss a technique that "probes" cortical states by examining behavioral and evoked potential responses to brief stimuli. When these "probes" are presented during a variety of well-developed SCP, they should produce differential responding: Probe stimuli presented during a surface-negative SCP should be processed more quickly by excitable cell assemblies as ignition of the corresponding cell assemblies would be facilitated. Shorter response latencies and higher amplitudes should result if the probes are processed in the same cortical regions that produce the SCP. During positive-going potentials, a reduced excitability of cortical neuronal networks should repress the processing of probe stimuli. However, the probe technique can only test the hypothesis derived from the model of threshold regulation to the extent that the source regions of both the SCP and the probe-processing are known. If both regions show little overlap, we cannot expect great interference. Furthermore, the cortical surface is not always parallel to the scalp and a surface negativity in the insula, for example, may show up as a positive shift on the central scalp. We can, however, expect a general facilitation of programmed motor responses when the surface potential has shifted in a negative variation, as the activity of many cortical areas converge to produce even a simple motor output. It is already known that simple reaction time is slowed by lesions in many cortical regions. Furthermore, we have put forward the conjecture that the P300, a transient slow positive shift, reflects a widespread "disfacilitation" that reduces excitability in the various cortical regions active during the baseline (Birbaumer & Elbert, 1988; Elbert, 1993), so that practically any response to additional stimuli presented during the positive shift should be inhibited. Although, there is currently little experimental evidence, theoretical considerations suggest that during the P300 there are depolarized "islands" in a sea of disfacilitation (see, e. g., Elbert, 1993). Magnetoencephalographic recordings and CSD of high-resolution EEG-recordings begin to confirm that P300 is not generated by one simple generator structure.

Negative deflections from the baseline show

task-dependent cortical and scalp distribution (Rockstroh et al., 1989; Rösler et al., 1995 a,b). The potentials evoked by simple probes or more complicated secondary tasks can be expected to show an area-specific processing as well. The latter distribution may or may not correspond to the enhanced excitability indicated by the SCP. The aggregate of initial (early) CNV, for instance, that is generated in areas of the frontal lobes might not affect the amplitude of the N100 generators in the auditory cortex, while the additional temporal generators of the early CNV (Elbert, Rockstroh, Hampson, Pantev, & Hoke, 1994), that are particularly prominent when the S1 is of auditory modality, should interfere with N1 production. Therefore, we also examined to what extent probe-evoked responses interact with the scalp distribution of the SCP.

The dependency of probes on SCP elicited in a primary task should not only be considered on the physiological level but should also be understood in psychological terms: Generally, the probe design comprises a *dual task*, which may provoke interference due to sharing attentional capacities (for review see, e. g., Navon & Miller, 1987; Pashler, 1994; Wickens, 1984). As repeatedly demonstrated, this competition for resources may lead to decrements in performance (summarized, e. g., by Klein & Taylor, 1994; Pashler, 1994; Shapiro & Raymond, 1994). Performance decrement seems to be most pronounced if the primary and secondary tasks require the activation of the same system. To give an example, Shapiro, Raymond, and Arnell (1994) found target recognition within serially presented visual information to be impaired for a period of about 360 ms beginning 150 ms after target presentation. This time interval corresponds to that of a positive SCP (see also McLean & Shulman, 1978; Posner & Klein, 1973). Within his "gating" model, Brunia (1996) expects larger evoked potential responses when intervening stimuli are of the same as compared to different modality. In the present studies, the impact of the dual-task on the interaction of cortical responses evoked by primary and secondary tasks was examined (a) by varying task demands associated with probe stimuli (requiring a fast button press or no motor response), and (b) comparing cross-modal and ipsi-modal stimulus conditions.

Finally, variations in SCP-distributions, threshold regulation, and attentional behavior in schizophrenic patients may allow for additional testing of the proposed relationships. Deviant patterns of SCPs (in particular smaller amplitudes of the P300, and the CNV, but larger amplitudes of postimperative negativity, PINV) have been reported repeatedly for schizophrenic patients (for summary, see Cohen, 1991, Pritchard, 1986), and have been related to dysfunctions of structures assumed to be involved in association formation and response control (e. g., Andreasen et al., 1990; Buchsbaum, 1990; Frith, 1993; Weinberger, 1995). The same structures, in particular the frontal cortex with its connections to basal ganglia, striatum, and temporal lobes, are also assumed to be involved in the threshold regulation of cortical excitation (Elbert, 1993). We consider the deviant patterns of SCP in schizophrenic patients to indicate deviant regulation of cortical excitability. In the present studies, we compared schizophrenic patients and healthy controls in order to explore to what extent the nature of SCPs as challenged by probe-evoked response is similar in schizophrenic patients and control subjects.

The results of six studies with probe-evoked responses will be summarized in the following paper and discussed in the framework of the assumed nature of SCPs as outlined above. Results will be arranged according to the concomitant background activity of the probe-evoked responses: P300, early and late pre-motor negativities (iCNV and tCNV) and postimperative negativity (PINV). Overviews of experimental details differing between the studies and over statistical effects are provided in Tables 1 and 2. Although only three of the six studies employed "probe" stimuli in the strict sense that stimuli did not require an overt response, we will use this term throughout the paper to avoid confusion.

Probe-evoked responses during the P300

Responses in an oddball task as "primary task" and responses to "secondary" probe stimuli were first reported by Woodward, Brown, Marsh, and Dawson (1991), who presented clicks at various intervals on 50% of the trials. Motor responses (button press) were significantly slower to clicks delivered 300 to 370 ms following target stimuli than reaction times to

Table 1 Methodological details of "primary" and "secondary task" across experiments.

Exp.	primary task	probe quality	response to probe	probe delays	probe-EP score	determined for probes at	probe-EP recordings
1	auditory oddball	5 ms, white noise 55 dB APL	button press	50%, 1/trial 260, 290 320, 350 380, 410 ms	80–300 ms	all probe delays	Fz, Cz, Pz
2	visual foreperiod RT task	400 Hz, 20 ms tone 80 dB	button press	50%, 1/trial 1.5 s pre-WS 0.5, 1.5, 2 s after onset 3 s after offset of WS	80–400 ms	all probe delays	Fz, Cz, Pz
3	identical to Experiment 2 (comparison of schizophrenic patients and matched controls)						
4	visual delayed-matching-to-sample task	20-ms white noise 50 dB	no response	1 s ISI	80–240 ms	baseline, iCNV tCNV, PINV	F3, F4, Cz C3, C4
5	identical to Exp. 4	identical to Exp. 4	no response	2/trial 2 s or 4 s ISI	80–240 ms	tCNV, PINV	Fz, Cz, Pz F3, F4, C3 C4, P3, P4
6	auditory delayed-matching-to-sample task	10 ms, 2 kHz tone 80 dB	no response	50%, 1/trial 1.5 s pre-WS 0.5 s pre-IS 1.5 s post-IS	80–300 ms	baseline, tCNV, PINV	as Exp. 5

clicks with other time delays and to clicks following standard stimuli. Raymond, Shapiro, and Arnell (1992) reported the (verbal) identification of a probe letter to be impaired if it occurred between 270 to 360 ms (depending on the particular experimental conditions) following a target letter within a "rapid serial visual presentation" paradigm. Closely following the study by Woodward et al., we examined responses to auditory probe stimuli ("secondary task") in Experiment 1 (see also Rockstroh, Müller, Elbert, & Cohen, 1992).

Methods

Subjects and design

Nineteen student volunteers were paid for participation. All subjects were right-handed as verified by a modified version of the Edinburgh handedness questionnaire (Oldfield, 1971). An auditory oddball task served as "primary task" to induce positive SCPs (P300). A total of 900 acoustic stimuli comprising 70% standard stimuli (1200 Hz, 55 dB) and 30% target stimuli (700 Hz) were presented at a constant interstimulus interval of 2.3 s. The subjects' primary task was to silently count the targets. As "secondary task," auditory probe stimuli were presented at different points in time before, during, and after the primary task. On 46% of the trials, clicks were presented as probe stimuli in addition to the standard or target stimulus; a probe could follow the onset of the stimulus at delays of 260, 290, 320, 350, 380, or 410 ms. A fast button press was required to every probe (secondary task). During the experiment the subject sat in a reclining chair within a partially sound-proof, electrically shielded and dimly lit subject-chamber. After preparation for the physiological recordings subjects received written instructions specifying stimulus conditions and tasks. Subjects were asked to adopt a relaxed position and to avoid head and eye movements. The experimental session lasted one hour.

Apparatus and physiological recordings

The timing of the experimental stimuli and the storage of reaction times and electrophysiological responses were controlled by an ASYST program (a scientific programming system for the control of experiments and data acquisi-

tion). Acoustic probe stimuli were brief (5 ms) white noise presented at 55 dB APL. Response buttons were easily manageable microswitches.

The EEG was recorded with a DC-amplifier (MES, Munich) along the midline from Fz, Cz and Pz referenced to the right earlobe. High-frequency cutoff was set at 30 Hz (6 dB/octave), bandwidth ranged from DC to 30 Hz. Nonpolarizable silver-silver chloride electrodes (ZAK) were fixed with Grass EC2 electrolyte as the conducting agent. The vertical and horizontal EOG were recorded with Beckman Ag/AgCl electrodes centered about 1 cm above and below the left eye and as near as

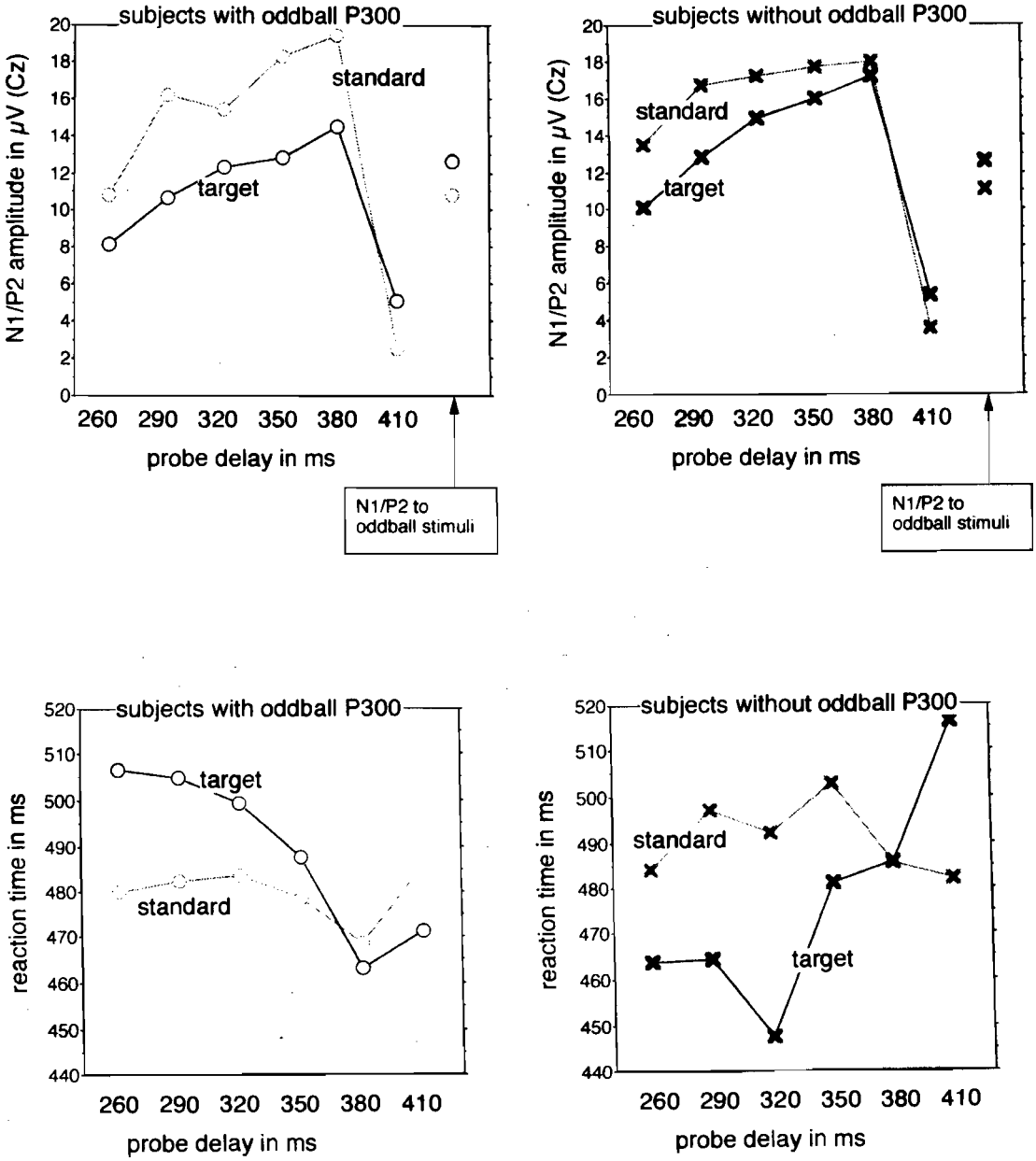

Figure 1 Peak-to-peak amplitudes of the N1/P2 vertex potential (top) and reaction times (bottom) averaged across subjects with (left) and without (right) oddball P300 separately for standard and target trials. The abscissa indicates the six different probe delays. (From: Rockstroh et al., 1992, with permission).

possible to the outer canthi. Beckman electrode jelly served as the electrolyte. The skin at all electrode locations was prepared by rubbing with abrasive paste (OMNIPREP). All data were digitized at a rate of 100 Hz and stored for offline analyses.

Data reduction and analysis

Trials with inadequate responses (errors or reaction time exceeding 1.5 s) were rejected from further analysis. For the remaining trials EEG epochs included a 100-ms baseline and 1400 ms following each stimulus. The data were controlled and corrected for artifacts following the procedure of Berg (1986). The P300 was determined as a score for the SCP evoked by the "primary task" as maximum positive deflection at the parietal recording within the latency range 250 to 400 ms following standard and target stimuli. Indices for *probe-evoked responses* were the evoked potential components N1 and P2, and the median reaction time (RT). As it was assumed that the probe-evoked potential would be "riding" on top of the SCP, point-by-point difference curves between trials without probes (as a "template") and the different probe conditions were calculated. From these difference curves the maximum negative deflection and the subsequent maximum positive deflection between 80 and 300 ms relative to a 100 ms interval prior to the probe were determined as N1 and P2 for the different recording sites.

In all experiments described in this paper, differences between groups, conditions, and recording sites were evaluated by means of analyses of variance (ANOVA). All reported *P*-values were obtained after adjustment of the degrees of freedom with the Greenhouse-Geisser-Epsilon. Means ± standard errors are presented.

Results

Eleven of the 19 subjects exhibited a pronounced parietal P300, whereas the other 8 subjects showed a fronto-centrally negative SW (nSW) that was substantially larger in response to targets than to standards. N1/P2 amplitudes to probes were smaller when the probes followed target and not standard stimuli. The difference was most pronounced when probes were presented 290–380 ms after stimulus onset, and subjects exhibiting an oddball P300 had a more pronounced N1/P2-amplitude attenuation than subjects with nSW instead of oddball P300 (see Figure 1). Similarly, subjects with oddball P300 responded slower to probes when a target-evoked positive shift was present, whereas subjects with "oddball nSW" responded faster to probes when a target-evoked negative shift was present. These results are in line with those of Woodward et al. (1991) and Posner and Klein (1973).

In Experiments 2 and 3 (see below), the N1/P2 to (auditory) probes presented 0.5 s after the onset of a 3-s visual warning stimulus eliciting a positive deflection (late positive complex, LPC), was significantly smaller than the N1/P2 to probes later in the 3-s anticipatory interval. This was true for healthy subjects (Rockstroh, Müller, Wagner, Cohen, & Elbert, 1993) as well as for patients with a schizophrenic disorder (Rockstroh, Müller, Wagner, Cohen, & Elbert, 1994). Subjects responded faster to probes presented between 1 s and 3 s after WS-onset than to probes presented before or 0.5 s after WS-onset. This suggests that inhibitory processes may last up to 500 ms and more. It may be argued, that the smaller or slower responses to probes following a "primary" stimulus are the consequence of resource allocation to the primary task.

Probe-evoked responses during anticipatory slow negativity (CNV)

Brunia and coworkers measured spinal reflexes and evoked potentials during phases of heightened attention and motor preparation (summarized by Brunia, 1993, 1996; Böcker, 1994). During the anticipatory interval of a signaled reaction task, tendon-reflex amplitudes but not reflexes elicited from the agonist were increased at the segmental level of the motoneurons mediating the response. Brunia (1984) concluded that a *general* motor facilitation is complemented by *specific* presynaptic inhibition of the Ia afferents. As pointed out by Böcker, "pre-synaptic inhibition is instrumental in motor preparation, because it prevents preliminary responses triggered by external stimuli, while supraspinal modulation is facilitated ..." (1994, p. 3). Böcker, Fortget, and Brunia (1993) examined the somatosensory evoked potentials (SEPs) to stimuli applied to

the responding hand prior to a signaled response, and observed a decrease of the P45–N70 and the N70–P100 but an increase of the P100–N140 amplitude. These authors considered the decrease of mid-latency SEPs to be a sign of specific response preparation (requiring inhibition), and the amplitude increase of later components related to a "general" facilitation. P45–N70 is known to be generated locally in the representational zones of the stimulated body surface in area 3b and in area 1. The more widespread P100–N140 amplitude showed the predicted enhancement with negativity. We would not expect this anticipatory negativity to be generated locally in these areas and therefore, the model of threshold regulation suggests that no attenuation should occur there. As mentioned before, gross levels of excitability must be controlled in the cortex. Therefore, depolarization in the motor cortex, the supplementary motor cortex, frontal association areas, and in the involved sensorimotor areas in particular, as seen during response preparation, might dampen activity in the unrelated somatosensory cortex and elsewhere.

Experiments 2–6 examined probe-evoked responses within the constant foreperiod paradigm. Cross-modal interactions with a visual "primary" and an auditory "secondary" task were examined in Exp. 2–5, tasks in the same (auditory) modality were evaluated in Exp. 6. Some studies have demonstrated a performance advantage, i. e., fewer errors and faster responding, to cross-modal stimulus presentation (see, for example, Wickens, 1984).

Methods

Subjects and design

Healthy, right-handed volunteers were paid for participation. In Exp. 2 (Rockstroh et al., 1993), a visual warning stimulus was presented for 3 s on 120 trials; a fast button press with the left hand was required to the offset of each WS. Counterbalanced across trials, an acoustic probe (400 Hz tone presented for 20 ms at 80 dB APL, 10 ms rise and fall time) could occur during the baseline (1.5 s prior to WS-onset), during the anticipatory interval (0.5 s, 1.0 s, 1.5 s, 2.0 s following WS-onset) and 3.0 s following WS-offset. No more than one probe was presented during a trial. Probe stimuli presented 3.0 s following WS-offset and 1.5 s preceding S1-onset served for comparisons with probes presented during the slow potential shifts. Subjects were asked to press a button, which they held in their right hand, as fast as possible in response to each click ("secondary task"). Of the total 120 trials, 25% (30 trials) were without a probe, in 25% of the trials, a probe could occur either at 0.5 or 1.0 s following WS-onset (15 trials each), 25% of the trials presented a probe at either 1.5 or 2.0 s delay from WS-onset (15 trials each), and 25% of the trials presented a probe 3.0 s following WS-offset or 1.5 s prior to WS-onset. Whether or not a probe was presented, as well as the points in time for a probe to occur, was determined by random order. The intervals between successive trials varied pseudorandomly between 6 and 10 s. The experimental session lasted one hour.

This design was modified in Experiments 4 and 5 (Klein, Cohen, Rockstroh, & Berg, 1996 a; Klein, Rockstroh, Cohen, Berg, & Dressel, 1996 b) in that the "primary task" consisted of a visual delayed matching-to-sample task. This modification aimed at inducing a postimperative negative variation. For the present paragraph, only the modification of the two-stimulus design will be described. The visual WS was presented for 100 ms, the visual IS followed after an ISI of 4 s. Ambiguity of matching was introduced by varying the size of the IS that had to be matched to the small or large diamond presented as WS, to between 40% and 60% of the difference between the two WS-stimuli. Ambiguous IS were randomly interspersed on 48 of the 144 trials in Exp. 4, and on 48 of the 204 trials in Exp. 5. Exp. 6 realized the delayed matching-to-sample task in the auditory modality (Rockstroh, Cohen, Berg, & Klein, 1997). Subjects heard 80 dB tones of 500 Hz and 1200 Hz, each of 80 ms duration and separated by 100 ms; one tone was presented to the left, the other to the right ear. The combination of tone-frequency (high-low), ear (left-right) and sequence (first-second) was counterbalanced within the 312 trials. After a 3 s ISI, one tone (IS) was presented binaurally for 100 ms; subjects were asked to keep in mind the tone frequency and the ear to which the particular WS had been presented and to press the left- or the right-hand button according to whether the IS matched the left-ear or the right-ear WS in frequency.

Another modification concerned probe stimuli: Auditory probes (50 dB clicks of 20 ms duration) were presented at regular 1-s intervals in Exp. 4, beginning 500 ms before the first WS; probe-EPs were determined for selected probes, i. e., during baseline (500 ms before WS-onset), tCNV (500 ms before IS-onset), and the postimperative interval (1.5 s after IS-onset). In Exp. 5 probes were arranged so that probes, two per trial, could occur 1.5 s before WS-onset, 0.5 s after WS-onset, 0.5 s prior to IS, and 1.5 s after IS. Thus, probes were separated by intervals of 2 s or 4 s. Probe-EPs were compared between the tCNV- and the PINV-interval. In Exp. 6, auditory probes (2000 Hz tone pips of 10 ms duration, 80 dB SPL) were presented on 50% of the trials; one probe could be presented per trial, either 1.5 s prior to WS, 500 ms prior to IS, or 1.5 s following an IS. Trials with and without probe, and trials with probes at the three different delays occurred in pseudorandom order. No motor response was required to probe stimuli in Exps. 4–6. The experimental sessions lasted for two hours.

Data acquisition and artifact control in Exp. 2 was the same as described for Exp. 1, but differed in Exp. 4–6 in that the EEG was recorded from midline and the lateral frontal (F3, F4), central (C3, C4) and parietal (P3, P4) sites. Visual stimuli in Exp. 4 and 5, and auditory stimuli in Exp. 6 were generated by the program GENTASK (NEUROSCAN) and presented on a visual display. As scores for the SCPs in the "primary" task, the initial CNV was determined as mean amplitude 0.5 to 1.5 s following WS-onset, the terminal CNV as mean amplitude 1.5–0.1 s prior to the IS. Indices for the probe-evoked responses were median RT (when probe detection had to be indicated by button press) and N1/P2. Although probe-evoked responses were determined from difference curves (as described for Exp. 1) as maximum negative deflection and subsequent maximum positive deflection between 80 and 400 ms following probe-onset relative to a 100 ms baseline prior to probes, in Exps. 2, 3 and 5, 6, data were filtered with a 3–7 Hz bandpass, and N1 and P2 were then determined as maximum negative deflection and the subsequent maximum positive deflection between 80 and 240 ms referred to the pretrial baseline in Exp. 4. This window was chosen after visual inspection of the filtered single-subject averages indicated that the probe-evoked deflections had returned to baseline level after 200 ms. N1, P2, and N1–P2 (peak-to-peak) amplitudes were determined for the midline and the lateral recordings over both hemispheres.

Results

The "primary task" induced a CNV in all experiments employing a two-stimulus design.

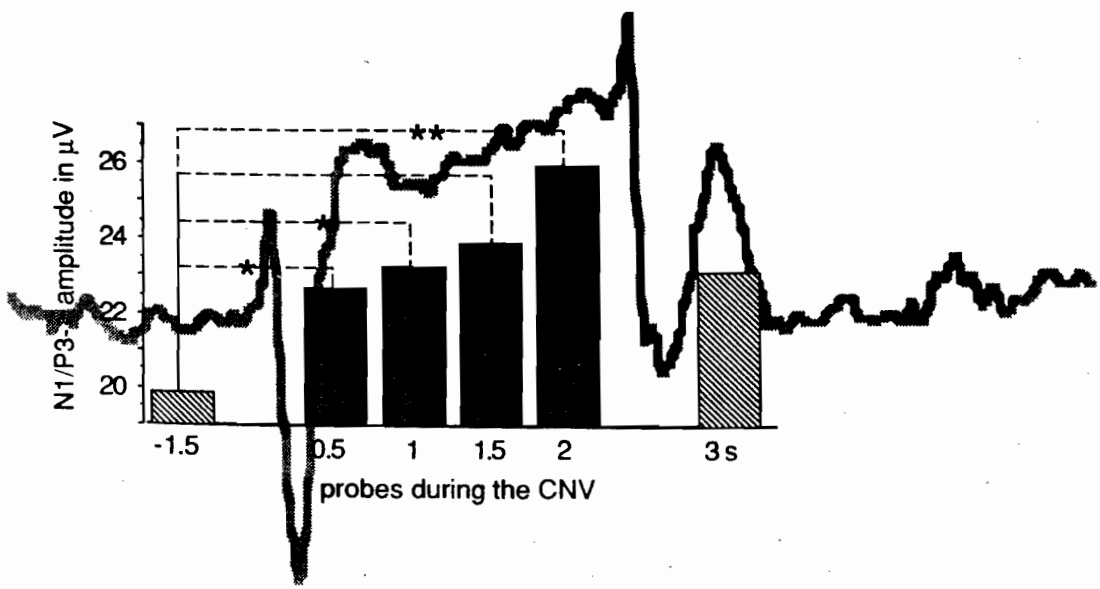

Figure 2 Grand average of SCPs evoked by the 3-s visual WS, and N1/P2 (peak-to-peak amplitudes in µV, bars) averaged across subjects separately for the probes presented at different time points during the constant foreperiod design.

Table 2 Statistical effects for N1/P2-amplitudes in the different experiments (see text for effects specific to a particular experiment).

Effect / Experiment	DELAY	GROUP × DELAY	TOPOGRAPHY	DELAY × TOPOGRAPHY
1	$F(5.85) = 51.4$**		$F(2,34) = 35.3$**	$F(10,170) = 16.8$**
2	$F(5,120) = 6.6$*		$F(2,48) = 65.5$**	
3	$F(5,105) = 4.8$**	n.s.	$F(2,42) = 11.5$**	
4	$F(3,45) = 3.3$t	$F(3,45) = 2.2$t	$F(4,60) = 10.8$**	$F(12,180) = 5.8$**
5	n.s.	n.s.	$F(4,80) = 7.5$**	$F(4,80) = 3.0$t
			F-C-P: $F(2,40) = 28.8$**	$F(2,40) = 5.9$*
			3-z-4: $F(2,40) = 25.5$**	
6	$F(3,69) = 11.5$**	n.s.	$F(4,92) = 24.1$**	$F(6,138) = 4.2$**

t: $P < .1$, *: $P < .05$, **: $P < .01$

An example is provided in Figure 2 (Exp. 2), which illustrates the average SCP, as well as the modulation of probe-evoked N1/P2. An increase in N1/P2-amplitude parallel to the development of the CNV is evident.

Larger N1/P2 amplitudes evoked by probes presented during the terminal CNV (*tCNV*) than in other time windows were found in all experiments, irrespective of the "primary task" or the specific experimental conditions (see Table 2 for statistical effects). This predominance was found for ipsi- (Exp. 6) and cross-modality of primary and secondary task, as well as, whether a motor response was required to the probe (Exp. 2) or not (Exp. 4 & 6). Compared to probe stimuli prior to the WS, N1/P2 was larger to probes presented 1 s and 1.5 s after WS-onset, i.e., during the initial CNV (iCNV). However, N1/P2 was larger in amplitude when elicited during the tCNV than during the less negative iCNV. Parallel to the larger N1/P2, motor responses were significantly faster, when probes were delivered 1 s and 2 s after WS-onset compared to the other probe delays, i.e., to probing outside of the CNV-window (Exp. 2, $F(5,120) = 3.4$, $P < .05$; Exp. 3, $F(5,110) = 3.2$, $P < .05$). The relationship between probe-evoked responses and the "background" CNV was further explored by correlational analyses in Exp. 5 and 6. In both experiments, larger tCNV amplitudes were related to larger N1/P2 amplitudes, with $r = .26$ ($P < .1$) in Exp. 5 and $r = .53$ ($P < .05$) in Exp. 6.

N1/P2-amplitudes were markedly smaller when the probe was not associated with a motor response, but showed the same increase in amplitude when elicited during the tCNV relative to baseline. When N1/P2 amplitudes were compared between recording sites with the largest amplitudes, they were largest where the CNV was largest – at Cz (see Table 2 for main effects TOPOGRAPHY and interactions TOPOGRAPHY × DELAY).

The modulation of probe-evoked N1/P2 during the anticipatory negativity does not seem to differentially affect its components, N1 and P2: In Exp. 2 and 4, the same experimental effects were obtained for the vertex potential, N1/P2, as for the N1 and the P2.

Taken together, the modulation of probe-evoked motor and cortical responses parallel to the development of anticipatory negativity (CNV), as well as the association of larger CNV and larger probe-evoked response support the hypothesis that negative SCPs indicate a state of heightened cortical excitability or excitation. Results were similar for experiments in which a motor response was required to every probe (Exp. 2 and 3) which might have induced allocation of resources to both tasks, and experiments in which no specific task was associated with the probes.

The functional significance of SCPs in schizophrenic patients

As outlined in the introduction, deviant patterns of SCPs in schizophrenic patients have been considered to indicate deviant regulation of cortical excitability mainly because structures related to schizophrenic dysfunctions are also assumed to be involved in the threshold regulation of cortical excitation. This hypothesis was challenged by examining evoked responses to probes presented during CNV and (as described in the following paragraphs) postimperative negativity.

Methods

Subjects and design

Groups of patients with a schizophrenic disorder and healthy controls matched for age, sex and level of education participated in Experiments 3–6. All patients were diagnosed using the Present State Examination (PSE, Wing, Cooper, & Sartorius, 1982) and met the DSM-III-R criteria for a schizophrenic disorder (295.1 and 295.3). Patients were in-patients of the local State Hospital. The current status of symptomatology was evaluated by the Brief Psychiatric Rating Scale (BPRS, Lukoff, Libermann, & Nuechterlein, 1986) during the week of the investigation. All patients were under neuroleptic medication. Control groups were selected to be comparable to the patient groups for age, sex and educational degree (results for control groups in Exp. 3–6 were reported above). It was assured that they did not take any psychoactive medication and had not been treated for neurological or psychiatric disorders. All subjects were right-handed as verified by a modified version of the Edinburgh handedness questionnaire (Oldfield, 1971). Subjects and patients received the same financial bonus for their participation.

The designs of Exp. 4–6 were described above, the design of Exp. 3 was identical to Exp. 2. Data acquisition, reduction and analyses were identical to the procedures described above.

Results

Modulation of probe-evoked responses with CNV did not differ between schizophrenic patients and controls, i. e., the interaction GROUP × DELAY for the N1/P2 amplitudes did not reach significance. Analyzing both components, N1 and P2, separately in a MANOVA in Exp. 3 resulted in an interaction GROUP × DELAY ($F(5,105) = 2.7, P < .05$): The generally attenuated N1-amplitudes of the patients did not vary between probe delays, whereas N1 increased significantly in controls. In the patient group compared to the control group, P2 was more positive at frontal and central sites (GROUP × ELECTRODE: $F(2,42) = 5.9$, $P < .01$) and increased significantly when probes were presented 2 s after WS-onset and 3 s after WS-offset relative to baseline ($F(5,105) = 2.4, P < .05$). In a group of schizophrenic patients, Wagner, Rendtorff, Kathmann, and Engel (1996) also found larger N1/P2 to probes during the tCNV than to probes prior to the WS, but patients – although exhibiting smaller N1-amplitudes than controls – did not differ from controls in the modulation of probe-evoked responses. In these studies, the N1/P2 evoked during the CNV showed a central maximum in schizophrenic patients as well as in controls. Although group-specific regulation of excitability was suggested by topographical differences (Rockstroh et al., 1994; Klein, Berg, Elbert, Cohen, & Rockstroh, 1997) with patients often exhibiting larger frontal iCNV and tCNV amplitudes and a more shallow fronto-parietal gradient than controls, no correspondence in the topography of probe-evoked responses was found. Thus, the comparison of schizophrenic patients and controls suggests that the functional meaning of anticipatory negativity (CNV) as enhanced cortical excitability is similar for patients and controls.

Probe-evoked responses during the postimperative negative variation (PINV)

A postimperative negative potential (PINV) is usually observed in schizophrenic patients but only under particular experimental conditions in healthy subjects, such as unexpected uncontrollability of the imperative stimulus (Rockstroh, Elbert, Lutzenberger, & Birbaumer, 1979), or ambiguity about whether stimuli can be controlled by adequate responding (Birbaumer, Elbert, Lutzenberger, & Rockstroh, 1986; Kathmann, Jonitz, & Engel, 1990; for summary, see Cohen, 1991; Rockstroh et al., 1989). It therefore may be related to uncertainty about the adequacy of one's own performance (Cohen, 1991), and reflect ongoing evaluation of performance and stimulus contingencies. This would mean that the PINV is a sign of increased excitation or it indicates expectation of further information similar to the negativity prior to the imperative stimulus. It is, however, not obvious that the enhanced PINV in schizophrenic subjects indicates the same process as that observed in controls under ambiguous conditions. This view is supported by a difference in the topographical pattern between the PINV in schizophrenics and the "uncontrollability" wave. Timsit-Berthier, Rous-

seau, and Delaunoy (1971) found reduced amplitudes of evoked potentials to probes presented shortly after the imperative signal in schizophrenic patients, and concluded that the postimperative negativity indicates active inhibition. In our experiments 2 and 3, probes during the postimperative interval (3 s after WS and response) elicited N1/P2 smaller than (Exp. 2) or comparable in amplitude to (Exp. 3) those elicited by probes 2 s during the WS and in anticipation of the response. Although healthy subjects in Exps. 2 and 3 did not exhibit postimperative negativity (see Fig. 2), some patients in Exp. 3 did. Against this background, experimental conditions in Exp. 4–6 were designed to induce postimperative negativity. In particular, ambiguity in the matching of an IS to the WS in the delayed matching-to-sample paradigm had proven efficient in inducing a PINV in schizophrenic patients as well as in controls (Klein et al., 1996 a).

Methods

Subjects and design

As described for Exp. 3, groups of (13–19) patients with a DSM-III-R diagnosis of a schizophrenic disorder were compared to groups of healthy subjects selected to be comparable to the patient group with respect to age, sex and educational level. As described above, the "primary task" consisted of a visual delayed matching-to-sample task, which was designed to modify postimperative SCPs. The visual WS was presented for 100 ms, the visual IS followed after an ISI of 4 s. Ambiguity of matching was introduced in the design by varying the size of the IS that had to be matched to the small or large diamond presented as WS between 40% and 60% of the difference between the two WS-stimuli. Ambiguous IS were randomly interspersed on 48 of the 144 trials in Exp. 4, 48 of the 204 trials in Exp. 5, and 72 of the 312 trials in Exp. 6.

Although auditory probes (50 dB clicks of 20 ms duration) were presented at regular 1 s intervals throughout the experiment, beginning 500 ms before the first WS in Exp. 4, two probes per trial were presented in Exp. 5. In Exp. 4 probe-EPs were determined for selected probes, i. e., during baseline (500 ms before WS-onset), tCNV (500 ms before IS-onset), and the postimperative interval (1.5 ms after IS-onset). In Exp. 5 probes were arranged so that probes, two per trial, could occur 1.5 s before WS-onset, 0.5 s after WS-onset, 0.5 s prior to IS, and 1.5 s after IS. Probe-EPs were compared between the tCNV- and the PINV-interval. No motor response was required to probes; subjects were instructed that they might hear

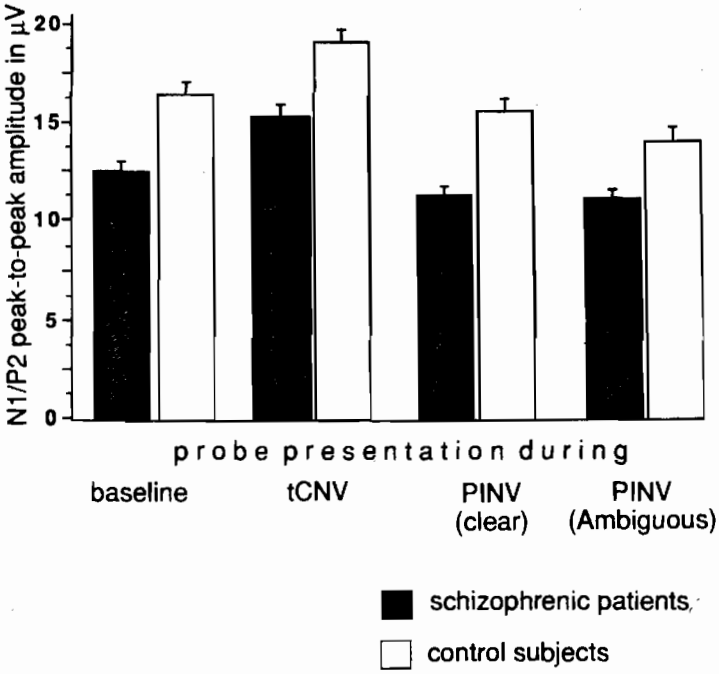

Figure 3 Vertex potential (N1/P2 peak-to-peak amplitude at Cz in µV, bars) averaged separately for the two groups (white bars: N = 13 control subjects, hatched bars: N = 13 schizophrenic patients) time points of probe presentation: baseline: N1/P2 elicited by probes 1.5 s prior to the WS; tCNV: N1/P2 elicited by probes 0.5 s before IS; PINV: N1/P2 elicited by probes 1.5 s after IS. PINV clear: probe-evoked N1/P2 were averaged across trials with clear matching of the auditory S2 to one of the auditory S1; PINV ambiguous: N1/P2 were averaged across trials, in which the S2 could not be matched to one of the S1-tones, conditions, which elicited the larger PINV. Data were obtained from Exp. 6 (Rockstroh et al., 1997, with permission).

"static" noises at irregular intervals which were not associated with their task to match WS and IS.

Data acquisition, reduction and analyses did not differ from the procedures described above. Respectively, 75% and 79% artifact-free trials entered analyses, without significant differences between groups. In addition to the scores for the anticipatory SCPs in the "primary" task described above, the postimperative SCP was described by the *PINV* determined as mean amplitude 0.5–1.5 s and 2.0–3.0 s following the IS.

Results

In these experiments, patients always developed a PINV, whether matching of the IS to the WS was clear or ambiguous, while controls exhibited a PINV only under ambiguous conditions. The N1/P2 to probe stimuli during the PINV was most pronounced at Cz (main effect TOPOGRAPHY, see Table 2). N1/P2 to postimperative probes was never larger than the N1/P2 to probes delivered prior to the IS, it was either similar (Exp. 4) or smaller in amplitude (see Figure 3 for an example obtained from Exp. 6).

Correlational analyses did not reveal a relationship between larger postimperative negativity and larger N1/P2 evoked during this postimperative negativity. For explorative purposes, the amplitudes of pre- and postimperative negativity were rank-ordered for every subject in Experiments 5 and 6. Then, the amplitudes of the corresponding N1/P2 at Cz were marked on the ordinate for the smaller and the larger negative amplitude. While there was a clear tendency for the larger N1/P2 to correspond with the larger negative SCP in control subjects in both experiments, the relationship was somewhat reversed in patients. Thus, irrespective of whether the CNV was larger in amplitude than the PINV or vice versa, the larger N1/P2 was found when evoked prior to the IS. This was found to be true for 53 of the 55 subjects examined, for schizophrenic patients as well as for healthy subjects.

In Exp. 4 and 5, tendencies for group-specific distribution of the N1/P2 evoked during the postimperative interval seemed to correspond to the distribution of the PINV: In Exp. 4, both PINV and N1/P2 tended to be larger in schizophrenic patients than in controls at frontal sites. In Exp. 5, both groups exhibited larger N1/P2 to probes during the PINV relative to probes during the tCNV at left-fronto-central recording sites (F3, C3). In the patient group, the difference between N1/P2 elicited during the tCNV and during the postimperative interval was smaller at frontal and larger at parietal sites than in controls (GROUP × DELAY × GRADIENT × ASYMMETRY: $F(4,80) = 3.6$, $P < .05$). However, these tendencies were not confirmed in Exp. 6.

Discussion

A comparison of results in studies employing *probe* stimuli in the strict definition of not being associated with an overt response and studies, in which the "challenge" stimulus was task-related, indicated larger evoked potential amplitudes to "challenge" compared to "probe" stimuli. It is possible that requirements of a motor response enhance evoked potentials to the response-related stimuli, as we also found larger target-evoked P300 in another study (Rockstroh et al., 1996), whenever target detection was indicated by a button press relative to target counting. It is also possible that a task related to the additional stimulus increased its impact and/or attentional resources allocated to stimulus detection, thereby increasing the evoked responses. On the other hand, the modulation of N1/P2 evoked by the additional stimuli did not differ whether the "probe" stimulus required an additional response or not, so that both "probe" and "challenge" stimuli can be discussed together with respect to their functional significance of "probing" a brain state.

As mentioned in the introduction, an impact of the dual task should explain differences between probe-evoked responses whether a motor response to probes was required or not. Discussion of performance measures in those studies comprising an overt response to probes must consider evidence and theory on dual task interference. According to the discussion of evidence for or against different types of competition in dual task situations by, e. g., Pashler (1994) or Navon and Miller (1987), a competition for processing resources in the sense of capacity sharing seems less likely given the easy task of button press to an easily detectable stimulus. Furthermore, Pashler (1994)

pointed out a characteristic of probe designs compared to secondary-task design (psychological refractory period) in that probe designs are sensitive to temporal uncertainty which would "masquerade as capacity limits" (p. 233). Outcome conflicts regarding the behavioral response also do not seem highly probable, as responses were not required within a critical interval. Outcome conflict or "cross talk" may, however, be assumed in that primary and secondary tasks both required attentional and motor preparation, thus, similar processing. In the same framework, we could also argue that the salience of the probe was reduced when no motor response to probes was required, thereby reducing cross-talk effects. In sum, the variation in probe-related reaction time between experiments is in contrast to the conclusion drawn from probe studies that "probe RT is substantially elevated when the probe is presented at approximately the time response selection in the primary task is likely to be under way" (Pashler, 1994, p. 234), but rather favors an explanation in the framework of enhanced or facilitated processing enabled by the neurophysiological state.

An alternative or additional explanation is provided by the concept of refractory periods: As pointed out by DeJong and Sweet (1994), performance may be impaired if two responses or tasks are presented with temporal overlap, impairment varying with advance preparation of both tasks, the degree to which second-task stimuli can be identified in parallel with the other task or the emphasis assigned to the task by instruction. Although the present conditions are different from those described by DeJong and Sweet, the present results could be interpreted in the framework of psychological refractoriness: (a) Responses in Exp. 2, although faster to the primary-task stimulus on average, were faster to the second-task (probe) stimulus that occurred 500 ms prior to the primary-task WS-offset. (DeJong & Sweet determined 650 ms as some upper limit for the psychological refractory effect, Pashler describes asymptotic course of SOA-PRP after 400 ms); (b) Second-task (probe) responses in Exp. 1 were delayed if stimuli were presented following auditory target detection (primary task) within 400 ms. However, as both tasks did not require effortful processing similar to tasks described, for instance, by Pashler, DeJong and Sweet, or by Navon and Miller, the effects of psychological refractoriness on performance were small. This is consistent with Pashler's conclusion that perceptual processing can operate in parallel with the performance of another task.

Physiological refractoriness may also have affected the probe-evoked potential. The major difference between experiments with and without probe-related behavioral response were larger N1/P2 amplitudes, when a button press to every probe was required than for the ignored probes. As a consequence of the regular presentation of probes at 1–4-s ISI each probe occurred in the refractory period of the preceding one. Substantial reductions of N1-amplitude to auditory stimuli presented within 10 s have been attributed to refractory effects (Roth et al., 1976). A magnetoencephalographic study (Mäkelä et al., 1993) demonstrated saturation of N1-amplitude at ISIs lasting as long as 8 s. Probe-intervals separated by 2 and 4 s, respectively, in Exp. 5 were partially successful in counteracting these problems, in that N1/P2 was larger (about 10 μV) compared to Exp. 4, however, still smaller compared to Exp. 2, 3 and 6 (above 20 μV). Exp. 5 revealed that probe-EPs were smaller during the 2 s (mean -7.5 ± 3.9 μV) compared to the 4 s (8.4 ± 4.7 μV, $F(1,20) = 5.4$, $P < .05$) interval, suggesting that probes separated by 2 s were affected by the refractory period. The longest interval between probes always included a baseline probe, and the largest N1/P2-amplitudes were found for baseline probes. However, while N1/P2 evoked during the baseline period varied (between 14 μV (Exp. 6), 20 μV (Exp. 2) and 24 μV (Exp. 3)), the N1/P2 evoked during the tCNV period was larger by about 6 μV in all these Experiments (Exp. 2, 3, 6). As the same amount of augmentation was found with (Exp. 2 and 3) and without (Exp. 6) a motor response, the latter might not critically affect the cortical response to probes presented during a state of increased excitability.

Primary and secondary tasks as realized in the present studies may be solved by different strategies, so that interindividual differences in strategies might affect the results. In the present studies, emphasis on the primary task was only induced by the instruction, which may not be sufficient to control for interindividual variability in strategies. An assignment of the

group difference in oddball-P300 or oddball-nSW observed in Exp. 1, for instance, to group-specific strategies cannot be ruled out. However, the groups did not differ with respect to the performance in the primary task, i. e., the number of correct counts of the target tones did not differ between subjects who developed an oddball P300 and those who did not. Furthermore, responses to the visual IS (primary task) were faster than responses to the (auditory) probes in Exp. 2 and 3, which would support the emphasis on the primary task even more, since faster RTs are usually observed following auditory stimuli.

Although N1/P2 amplitude varied across the WS-interval and reached its maximum when elicited during the tCNV in all experiments, results for the probe-evoked response during the postimperative interval, parallel to the PINV are inconsistent: similar amplitudes of N1/P2 elicited during tCNV and PINV in Exp. 3 and 5 suggest that both SCPs have a similar meaning. On the other hand, two studies explicitly designed to provoke a PINV found smaller N1/P2 during the PINV-interval (Exp. 4 and 6). A comparison of the consistently most pronounced probe-evoked potential during the CNV-interval and the (inconsistently) smaller probe-evoked potential during the *PINV*-interval suggest different conclusions:

1) Anticipatory and postimperative negativity do not represent comparable enhancement of cortical excitability. Different brain regions contribute to the generation of PINV. This might explain larger probe-evoked responses during the CNV than during the PINV. Dongier (1969) and Timsit-Berthier et al. (1971), for instance, suggested that the PINV indicates active inhibitory processes.
2) The larger N1/P2 evoked during the tCNV might be the consequence of an increased attentional state in anticipation of the task-relevant IS, so that any input during this state is processed already as efficiently as the anticipated IS. However, attention can well be associated with increased cortical excitability in psychophysiological terms (Rockstroh et al., 1989).
3) Processing of the secondary task may have been inhibited during the first 1–2 s following the processing of a relevant stimulus, in this case the stimuli associated with the primary task. This might be explained as a consequence of the psychological refractory pe riod (DeJong & Sweets, 1994; Pashle 1994) or by resource allocation model (e. g., Navon, 1985; Navon & Gopher, 1979 suggesting that such processing requires re source distribution, and reduces the re sponse to the secondary task, while "genera attention" in anticipation of the IS facili tates responding to primary and secondar stimuli. Strayer and Kramer (1990) foun performance decrement and reduction o P300 amplitude only when dual-task condi tions required equal emphasis of the task Sternberg and running memory (see als Wickens et al., 1983). The smaller N1/P2 t probes following the WS and the IS relativ to probe-N1/P2 during the CNV may indi cate this psychological refractoriness Again, we would emphasize that the de scription on the psychological and the phys iological level, e. g., mechanisms of atten tion and threshold regulation, are two side of one coin that may be mapped onto eac other.

The similarity of results between studies wit cross- and ipsimodal primary and secondar tasks is not in line with the hypothesis that fa cilitation occurs only in cross-modal dual task (Brunia, 1996). The similarity of results be tween studies with cross- and ipsimodal prima ry and secondary tasks rather suggest a gener ally facilitatory nature of negative SCPs.

Schizophrenic patients and healthy control did not differ in the modulation of probe evoked responses, suggesting similar relation ships between slow and evoked brain activity in patients and controls. This, however, may no hold for the PINV. Findings of smaller N1/P parallel to larger PINV in patients are intrigu ing. They might support the hypothesis of a inhibitory nature of the PINV, particularly i patients (Timsit-Berthier et al., 1971). Howev er, it seems necessary to consider the locatio of the PINV generators when evaluating th relationship between evoked and slow poten tials. Berg et al. (1996) determined two bilater al generator structures of the PINV, one locat ed frontally, the other being strongly relate to the CNV-generator. A modality-specifi fronto-central or centro-parietal, respectively PINV was described by Rockstroh et al. (1997) when the PINV following ambiguous stimulu

matching was referred to baseline, whereas a modality-nonspecific frontal PINV was found only in schizophrenic patients when the PINV was referred to CNV-amplitude. If the orbitofrontal cortex contributes significantly to the PINV, the latter should be a positive potential on the surface of the orbitofrontal cortex and consequently would be seen as negative scalp potential over frontocentral regions. An alternative generator structure might be assumed in the cingulate gyrus. Obviously, the source location of PINV generators should be determined before the relationship between PINV and N1/P2, that is mainly generated in the auditory cortex, can be described more precisely. The lack of a difference in probe-evoked responses between patients and controls may also be attributed to the state of the patients examined in the present studies: All patients were under neuroleptic medication and beyond an acute state allowing them to follow the instructions of the complex stimulus and task conditions without problems. No significant correlations were found between electrocortical indices (SCPs and probe-responses) and BPRS ratings of symptomatology. Thus, the similarity of probe-evoked responses between groups in the present studies may be interpreted as a consequence of medication and improvement of symptomatology. If so, the functional significance of SCPs as evaluated by probe-responses would be state-dependent and not indicative of a disorder-specific dysfunction. Clarification of this question would require comparing medicated and unmedicated patients and/or patients in different stages of illness. On the other hand, schizophrenic patients in their acute stages of illness are usually distracted and unable to meet the attentional requirements of experiments as described above, so that results may be influenced by such state-dependent distractability as well.

The covariation of probe-evoked responses with the amplitude of SCPs provides further support for the idea that the dynamics in physiological (SCPs) aspects reflect psychological concepts (attention) to a greater extent than a single subunit (i. e., ERP-component). Furthermore, results of the patient studies suggest that the same psychophysiological relationship can be assumed for a range of psychological and psychopathological conditions. Patient studies also revealed that CNV and PINV may be different in nature; however, the presently employed experimental approach did not allow clarification of this relationship in psychopathology any further.

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