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Connections between studies of the neurobiology of attention, psychotic processes and event-related potentials

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My aim in this article is to briefly summarize some of the biological concomitants of attention, to point to putative anomalous dysfunctions of these processes in schizophrenia and to show the relationship between these and what some event-related potentials (ERPs) may measure.

Attentional schemata

Let us first try to understand the ways in which the term attention is used. We may distinguish 3 views. Firstly there is a simple generalization that helps one focus on the problem (see box, Fig. 1): attention is 'the selective aspect of perception'.

The second and third views may be called the top-down and bottom-up approaches. The top-down approach represents the application of the working hypothesis (Fig. 1). It prescribes constraints for the measures one can make. The most important division here is between sustained attention (concentration and vigilance over time) and selective attention (allocation of channels for carrying information for further processing). At the bottom of the diagram are various dimensions one can measure, whose function determines the efficacy of the process.

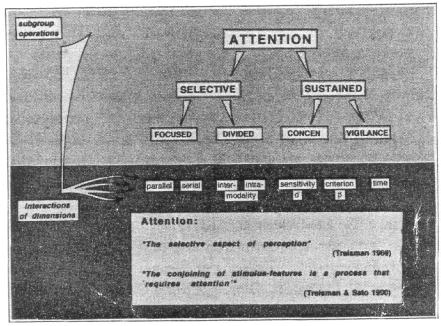

Fig. 1. 'Top-down' scheme of attentional operations with a selection of contributing and interacting dimensions that can be experimentally manipulated or measured.

The bottom-up approach represents an attempt to synthesize an attentional mechanism through an assembly of the observations of functions, and hence the operations that have to be taken into account. Many of these were ably summarized by Johnston and Dark (1986, Table I). One of the more enduring metaphors in this work refers to the analogy of an adjustable beam-spotlight (number 5).

Whichever approach one prefers, we should not overlook that there are certain spheres of more general psychobiological function that in practice affect the way attentional mechanisms perform.

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TABLE I

SELECTIVE ATTENTION: TEN EMPIRICAL GENERALIZATIONS REFLECTING THE LITERATURE UP TO 1986

W.A. Johnston and V.J. Dark, *Ann. Rev. Psychol.*, 1986, 37: 43–75.

1. All levels of stimulus analysis can be **primed** for particular stimuli.
2. Selection based on sensory cues is usually superior to selection based on **semantic** cues.
3. **Irrelevant** stimuli sometimes undergo semantic analysis.
4. **Spatial** cues are especially effective cues.
5. Attention is independent of eye fixation and can assume the characteristics of an **adjustable-beam spotlight.**
6. Stimuli outside the spatial focus of attention undergo little or no semantic processing – is restricted mainly to simple physical features.
7. Overlapping objects can be selectively processed.
8. Non-selected objects within the spatial foci of attention undergo little or no semantic processing.
9. Selective processing is sometimes performed **passively** and sometimes **actively**.
10. Selective attention can be guided by active schemata.

Mirsky and Orren (1977) described 3 such spheres – consciousness, sleep-wakefulness and orientation-habituation. Together they strongly influence arousal, vigilance, attention and adaptive interactions of the organism with the environment.

Cutting across these schemata are numerous attempts to describe the functional *mode* of attentional mechanisms. These account for numerous observations in terms of categories of characteristics that in turn allow predictions for more detailed experiment. They are thus heuristically useful but intellectually limited by the constraint of the dichotomy they erect. Examples include serial *vs.* parallel processing, active/passive or automatic/controlled processes, stimulus-/response-set, sensory-/concept-driven, open-/closed-loop or exogenous/endogenous control of processing (Straube and Oades 1992 and references therein). Suffice it to say, in this short overview, that one can imagine a concept-(experience)-driven selection proceeding 'automatically' and, depending on the demands of the situation, involving either serial or parallel processing.

For someone setting out to investigate biological measures associated with selective attention the model elaborated now 20 years ago by Kahneman (1973) is still useful (Fig. 2). Some advances in ERP research can be usefully placed against the background of this model even though it is biased toward serial processing schemes. Thus, for example, we can see that dimensions of a stimulus may be processed hierarchically according to perceptual difficulty, as was demonstrated with measures of processing negativity (PN), where locus in a dichotic paradigm is processed faster than pitch (Hansen and Hillyard 1983). But fundamental to the design of most modern studies of selective processes is the emphasis on the adaptive rather than the salient aspect of the stimulus: the ability to discriminate a stimulus that is *relevant* to the

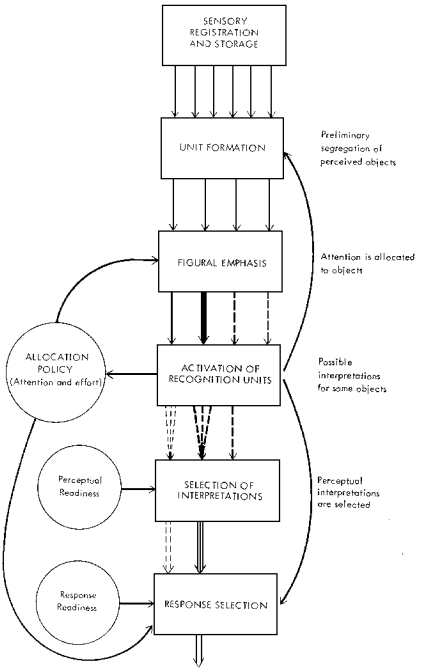

Fig. 2. Kahneman's scheme (1973, with permission) illustrating interactions of perceptual mechanisms and attentional processes.

organism and situation from one that is *irrelevant* (Posner and Boies 1971).

Neurobiology of attention

In moving from the *phenomenon* of attention to the *medium* it is important to emphasize that the origins of CNS-contributions are widespread but the *component* mechanisms may be more localized. To see the relations between the two it is essential to recall the basic anatomical basis for the incoming flow of information. Refinements (e.g. fronto-temporal crosstalk) or interpretations (e.g. control diagrams) represent later developments and are the consequences of specific experiment.

Specific sensory information ascends through the thalamus (Fig 3). Here there are collateral links with the non-specific nuclei mediating intervening variables such as wakefulness. Information that has gone on to association cortices may elicit a 'gating'-like feedback at the level of the thalamus. This type of effect is shown by ERP records (e.g. Hackley et al. 1987) of attentional effects on components as early as 20 msec. The anatomical links for feedback may be remarkably specific: Siwek and Pandya (1991) showed links between small sub-groups of cells in prefrontal and *mediodorsal thalamic areas*, (e.g. area 9, 10 with the most dorsal part of the nucleus).

As the P1/P50 is usually accepted as reflecting the passage from thalamus to the relevant primary cortices and N1-associated components, the subsequent distribution to appropriate associative areas (Knight et al. 1988), we should note two striking findings at this level in schizophrenia.

The first concerns prepulse inhibition (PPI). The normal ability of a soft sound to interfere with further processing of a loud noise *c.*100 msec later, as indexed by the P50, is reduced in schizophrenics. Even though the size of the basic startle effect may depend on DA activity, the tuning effect involved here is normally associated with decreased NA activity (see below). A schizophrenic group studied by Waldo et al. (1992) did not modulate their NA activity. PPI is usually reduced in acute psychosis (including mania), but not in obsessive-compulsive disorder (Schall et al. submitted).

The second confirms that the areas and connections active at the P50-N1 latency can function

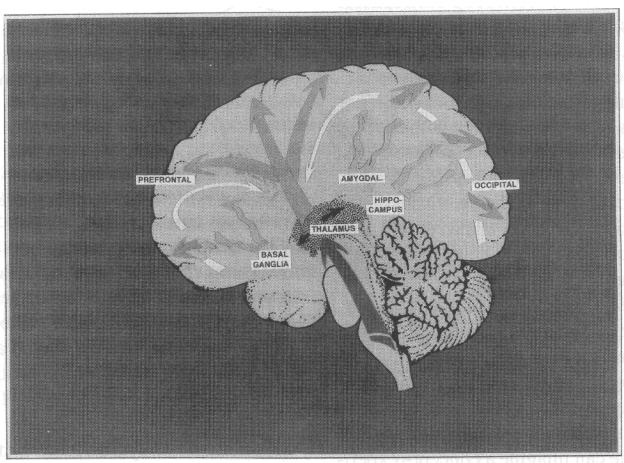

Fig. 3. Illustration of the flow of sensory events through several stages of processing in the brain: *note*; 1, ascent through the thalamus (collateral interaction) to primary sensory cortices; 2, allocation to association cortices (potential for feedback control); 3, subcortical loops (e.g. basal ganglia, thalamus, amygdala, hippocampal complex); modulation by long-axon ascending aminergic systems (e.g. DA, NA, 5HT, ACh) not shown.

differently in schizophrenia. Thought disorder in disorganized schizophrenics (i.e. without psychomotor poverty or reality distortion) shows a positive correlation with increased blood flow (rCBF) in the *mediodorsal thalamus* and frontal Brodmann areas 9, 10, 24, 32 and a negative correlation with areas 39, 44, 45, 47 (Liddle et al. 1992).

As we progress from N1 events, information is relayed to appropriate association areas of the cortex allowing for conscious/controlled processing. Relays via subcortical nuclei (e.g. pulvinar) allow for automatic processing (cf. blindsight). The latter type of processing may well be illustrated by P2 components, often associated with inhibitory processes essential for the rejection of common events in oddball discriminations (Alho et al. 1987). The influence of stimulus features on this process, particularly in primary sensory cortex, may well incur 5HT activity (Hegerl and Juckel 1993).

For processes associated with events around the P3 latency there are at least 3 other classes of subcortical comparison necessary (see wavy arrows, Fig. 3). These may be listed as three checks:

1. What are the needs? (state, motivation), use of the uncinate fasiculus (orbito-frontal-amygdala-hypothalamus);
2. What are the stimulus associations? (target, landmark, shock); use of parahippocampal gyrus;
3. Is an appropriate response pattern available? use of basal ganglia.

The first system shows hypoperfusion in disorganized schizophrenics, the second a left-right asymmetry in reality-distorted subjects and the third hyperperfusion in those with the poverty syndrome (Liddle et al. 1992). It is thus no wonder that if P3 reflects such a range of neural activity that it is weakly or variably expressed in schizophrenics and other patients with mental disturbance.

One implication of the distributed processing indicated by the wavey arrows in Fig. 3 is that there is much cross-talk between widely separated parts of the brain and that the outcome, expressed as ERP generators may also be widely distributed. Thus it should be no surprise that temporal lesions may interfere with negative components usually maximal in frontal regions (Woods et al. 1987) and that frontal damage may interfere with P3, usually maximal at parietal sites (Nasman and Dorio 1992). (For a recent discussion on multiple P3 generators see Johnson 1993.)

The generators are *per se* temporary representations of the stage of stimulus processing and reflect the outcome of neural interactions. This is a phenomenon reminiscent of long-term potentiation (LTP) – a facilitation of neural activity dependent on amino-acid transmitters (e.g. Asp and Gly) and enhanced by rhythmic burst firing, especially at theta frequencies (Bliss and Collingridge 1993). As theta frequencies are more common in man than was thought until recently (e.g. Michel et al. 1992) and have long been associated with attention-related function in animals (see below) it is relevant that significant components such as the N1, N2, P3 and late negative wave tend to occur in phase with a theta rhythm. Others have also reported enhanced theta frequencies during increased attentional demands in ERP-oddball studies (Basar-Eroglu et al. 1992). The hippocampal complex, one source of theta waves, figures prominently in analyses of rCBF designed to find 'the common factor' among schizophrenics with different symptoms (Friston et al. 1992) and in theories of the schizophrenic process (Gray et al. 1991).

Subtraction and comparison in the physiology of attention

The rCBF measures from the Hammersmith cyclotron unit just mentioned emphasized the left medial temporal lobe for an association with the psychopathology of schizophrenia. This is also the region where McCarley and colleagues (1993) have elegantly shown reduced volume on magnetic resonance images, a reduced P3 in auditory discrimination and an association with thought disorder in schizophrenic patients. The link to attention is brought even closer by the report from Posner et al. (1988) that schizophrenic subjects *with active symptoms* were relatively slow to detect targets in the right visual field, reflecting left-hemisphere function. This task places demands on the ability to switch attention, a putative role of DA activity (see below) – a transmitter also reported to be

anomalously high (reflecting low activity) in post-mortem samples from the left temporal lobe of schizophrenics (Reynolds 1983).

Friston et al. (1992) also emphasized the frontal connections in their rCBF analysis. It is in the dorsolateral prefrontal and cingulate regions that Petersen and colleagues (Corbetta et al. 1991) found residual rCBF activation in healthy subjects after subtracting brain images derived during passive focussed attention from those obtained under conditions of divided attention. The cingulate is also activated during performance of the incompatible condition of the Stroop test (Pardo et al. 1990: i.e. read the color of the ink of a word spelling another color). Disorganized schizophrenics more than others have problems on this part of the Stroop test and it is this group which shows hypoperfusion of the cingulate (Liddle et al. 1992).

In the foregoing paragraphs strikingly mutually supportive results on limbic function appear from the comparison of modern imaging techniques (MRI, PET and ERP), attempts to dissect attentional mechanisms using tasks with specific demands and use of schizophrenic subgroups defined by symptom cluster rather than diagnosis.

I report briefly an exploratory analysis using this type of approach. Two subtraction waves, mismatch negativity (MMN) and difference negativity (Nd) derived from the passive and active phases of a 3-tone oddball discrimination were compared. The principle resembles Petersen's subtraction of PET-metabolic measures derived under different stimulus-processing demands. The MMN is the subtraction of ERPs elicited by common (0.8 KHz) from rare deviant standard tones (2.0 KHz) under passive non-attentional conditions. The mismatch registered represents the difference in pitch and frequency. The Nd is the result of subtracting ERPs elicited by a rare 1.4 KHz tone in the passive condition from the same tone used later as a target for response.

The MMN is seen as representing a short-term stimulus-trace-memory (Näätäen 1990) reflecting a largely automatic comparison process (pace Woldorff et al. 1993). It was recently reported to be markedly reduced in a heterogeneous group of schizophrenics (Shelley et al. 1991). We confirm this in Fig. 4 and show that the attenuation is marked for both paranoid and non-paranoid groups whether defined by clinical diagnosis or *active symptoms* scored after the test in a semi-structured interview. Further we show that there *is* a difference between sub-groups, but only if they are separated by *active symptoms*. In the paranoid group MMN is halved but this tends to be more than in the non-paranoid group where MMN is >75% attenuated at frontal sites. In the context of the emphasis above on reports of anomalous temporal lobe function, it is of interest that particularly those schizophrenics without paranoid symptoms show an anomalous negativity at the T6 site (and less so at T5: Fig. 4).

In contrast to the MMN, Nd is present in both schizophrenic sub-groups (Oades et al. 1993). But if the groups are separated by symptoms, Nd is significantly attenuated over left frontal/right parieto-temporal sites in paranoid and over right frontal/ left posterior parietal sites in the non-paranoid group (Oades et al. 1994).

This result, obtained with teenaged patients soon after admission, cannot exclude a potential influence of medication. The same subjects performed a conditioned blocking task. This tests the extent to which they learned about a superfluous stimulus that was nonetheless relevant to task-solution. While most paranoid patients performed relatively normally, ignoring the redundant stimulus, non-paranoids often showed attenuated blocking. However the non-paranoid group also showed increased DA utilization, as measured in 24 h urine samples

Fig. 4. *Top:* Bilateral symmetric fronto-parietal distribution of MMN in healthy subjects (200–260 msec: *see text)* scale +3.0 to –4.1 uv. Alongside t-test differences are compared to paranoid (P) and non-paranoid (NP) schizophrenics (line shows t(31) 1.7, $p < 0.05$). *Left:* MMN in schizophrenics diagnosed as paranoid (12) and non-paranoid (16): A) MMN at 6 sites (bin 4 msec), B) topography 200–260 msec (scale +2.4 to –2.5 uv), c) no significant t-test differences between psychotic groups (200–260 msec). *Right:* MMN in schizophrenics with active paranoid symptoms (13) (rated post-test by median split of SANS-SAPS scores) *vs.* non-paranoids (15). A) B) *as above*, C) t-tests between psychotic groups $p < 0.05\%$ at frontal sites (P > NP), T3 and T6 (NP > P).

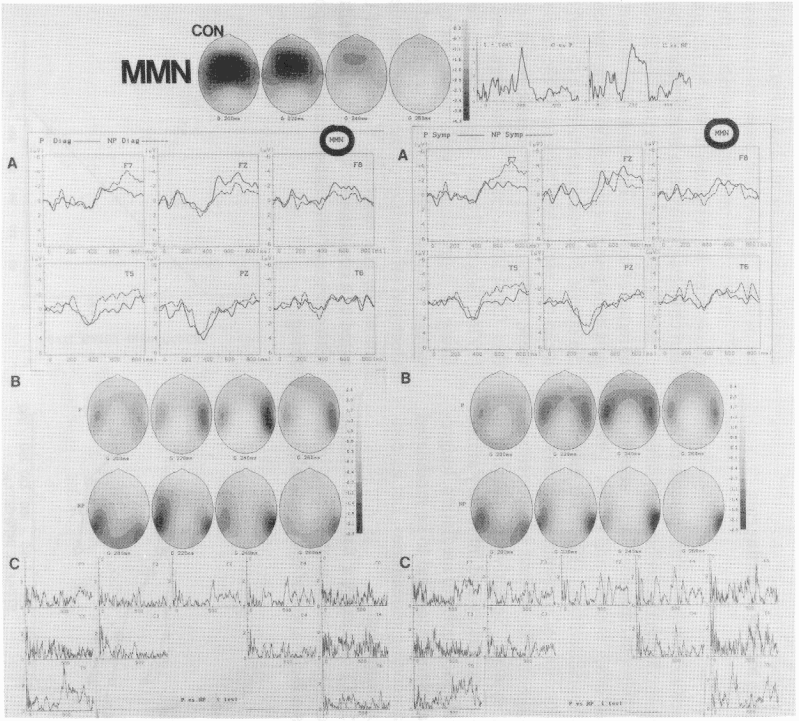

Fig. 4. See previous page for legend.

(Oades et al. 1992). Increased DA and NA activity may reflect that their response to medication had not entirely stabilized. Independent of the biochemical dimension it appears that acutely ill schizophrenics can experience problems in determining stimulus-relevance, as has also been reported with the related latent inhibition task (Baruch et al. 1988).

Signal processing and monoaminergic modulation

I have just implied a DA role in schizophrenic problems with attention. From the problems of schizophrenics with thought disorder and attention (reviews: Oades 1982; Straube and Oades 1992) and from basic considerations (Fig. 3) it may be assumed that a number of transmitter systems are involved in mediating the several components of an attentional system. Selective processing is bound to involve excitatory and inhibitory amino acids in relatively local cortical mediation, longer-loop subcortical comparison and to be modulated by long-axon ascending monamines. Let us consider the monoamines first.

Serotonin (5HT) can exert a form of volume control. Deliver a pulse burst to the raphe in the cat and there is a facilitation of the potentials one can evoke in the hippocampal perforant path 5–140 msec later. This effect depends on the state of wakefulness (Trulson and Jacobs 1979; Srebro et al. 1982). The interval is one relevant to the elicitation of LTP and approximates the theta frquency. It is possible to predict learning speed in rabbits from small changes of theta (Thompson et al. 1980). Small decreases of theta frequency follow toxic raphe lesions and increases follow raphe stimulation (e.g. Graeff et al. 1980, Fig. 5). This illustrates one aspect of the potential involvement of 5HT in selective processing, which as mentioned above may be reflected in the N1-P2 amplitude and changes of this seen in psychiatric patients.

Noradrenaline (NA) function is often described in terms of tuning. There must be at least two inputs to a given brain region vying for control of the output. NA biases the relative control of activity in the region and thus tunes the response (review, Oades 1985). The classic report leading to this formulation came from Segal and Bloom (1976). Essentially they found that suppression of firing of hippocampal cells in the rat by a tone would habituate, but could be reinstated through electrical stimulation of the locus coeruleus, origin of the NA innervation. However if the tone acted as a conditioned stimulus, then pairing tone with coeruleus stimulation increased hippocampal firing.

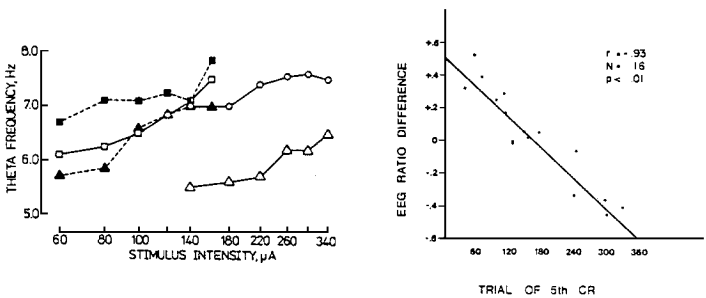

Fig. 5. *Left:* Increasing frequencies of hippocampal theta rhyhtm produced by increasing intensities of electrical stimulation of the median raphe (50 Hz, 0.5 msec, 5 sec train). Each point is the mean of two tests in one session or an individual rat. (From Graeff et al. 1980 with permission of the author and Pergamon Press.) *Right:* Scatterplot and regression line showing a significant relation between changes in the ratio of high to low EEG and the number of training trials required to attain the 5th conditioned response. Pre-task EEG samples showed the more theta, the faster the learning raste r = +0.72: task, – conditioning nictitating membrane response to air puffs in the rabbit. (From Thompson et al. 1980 with permission of the author and publisher.)

Recent ERP work supports this interpretation (Shelley et al. 1994). Healthy subjects were required to detect a stimulus of a particular pitch and duration from one ear. Under clonidine, which decreases NA firing, normal hierarchical processing was disrupted and the hit-rate decreased. Important here is that while easy processing according to stimulus locus was unaffected, further processing according to the more difficult features of pitch was specifically impaired – namely the middle-PN elicited by irrelevant features (alone) increased. This suggests that noise in the signal to noise comparison was not tuned out.

Dopamine (DA) activity (implicated in attention, motivation and motor organization alike) has been described as promoting the likelihood of a switch occurring between two inputs competing for control of the output of a DA innervated region (Oades 1985). The argument was initially made from psychopharmacological modification of operant discrimination, of animals' escape strategies from a water tank (Van den Bos et al. 1991) and of food-search strategies on a holeboard. For example, deviations from learned hole-visit sequences resulted from increased mesolimbic DA stimulation as a result of direct ventral tegmental treatment with neuroleptic (Oades et al. 1985) or hippocampal damage. In the latter cases systemic neuroleptic treatment resulted in mild improvements (Oades and Isaacson 1978).

Recent ERP work supports the interpretation. In the dichotic paradigm used by Shelley and colleagues (above) the neuroleptic droperidol resulted in a decreased hit rate and decreased PN in the middle and late latency range (not stimulus-specific). This suggests that subjects discriminated the easiest aspect of the task (locus) and locked on to the solution, leading to impaired comparisons according to stimulus pitch and duration.

In mild Parkinsonism where DA is lacking (extrapyramidal motor system) L-DOPA treatment may help discrimination performance. Reaction times shorten. But it may induce an imbalance and even hinder cognitive function if the task is simple and one should 'lock on' to the solution. P3 latencies lengthen (Prasher and Findley 1991). In contrast if subjects are asked to detect a spot on a screen, where the position varies on each trial (Fig. 6)

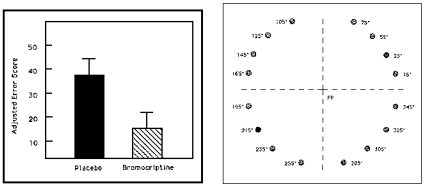

Fig. 6. *Right:* Possible location of 16 randomly presented visual cues for delayed learning task. The display showed the fixation point (FP) but not the marked quadrants. Trial sequence: FP 3 sec, cue <200 msec (10' eccentricity), time out (black-screen) 0–8 sec, subject points to cue locus, inter-trial-interval 2.5 sec. *Left:* Mean errors (+sem) on delayed learning task significantly decrease after 2.5 mg bromocriptine with respect to placebo ($t(7)$ 2.9 $p < 0.02$). (After Luciana et al. 1992 with permission of the author and publisher.)

and remember it for 0 or 8 s, then a good deal of cognitive flexibility is required in the formation and changing of working memory specifications (Luciana et al. 1991). This delayed learning ability is known to depend on neuronal activity in layers V and VI of the prefrontal cortex and to be influenced by DA receptors there. In this demanding task the performance of women was improved after treatment with bromocriptine, an agent with D2 agonist properties.

A word of caution on the generalization of these results to schizophrenic mechanisms should be made. Ward et al. (1993) in a similar paradigm to Shelley et al. (above, the same research group), reported decreased PN in unmedicated schizophrenics that related to the degree of psychopathology shown. Does this show that the same effect as the neuroleptic in healthy subjects can be achieved by the biological concomitants of psychosis or do both groups show decreased DA activity? Our own experience with the 3-tone discrimination in medicated schizophrenics is different. Firstly PN was present in psychotic patients, secondly it was shifted parietally in paranoid subjects. Does this imply that medication counteracted the impairment or is the 'PN' reflecting different processes in the two paradigms?

In the 80 years since *acetylcholine* was identified as a neurotransmitter a huge literature has built up showing that its activity in the CNS is essential

for efficient learning and memory. This has largely resulted from evidence of interference from cholinergic antagonists; the effects of cholinergic agonists have been less than convincing and deterred a formulation for a 'cholinergic role'. However a series of ERP studies using visual discriminations of varying difficulty by Callaway, Halliday et al. showed that antagonists like scopolamine slow N1, P3 and often reaction time, interfering particularly if the task was relatively easy and more so with the target than the irrelevant stimulus (Brandeis et al. 1992). This led them to suggest that cholinergic activity promotes parallel processing and the more automatic processes by which salient features capture attention.

The widespread involvement of inhibitory (e.g. GABA, Gly) and excitatory *amino-acid* transmitters (e.g. Glu, Asp) in local circuitry in association areas as well as in some long feedback loops (e.g. basal ganglia) implies their inevitable participation in the generation of ERP components and comparator processes essential to attentional mechanisms. It is therefore surprising when anticholinergics and neuroleptics can affect several ERP components, respectively monotonically or differentially, if an agent such as diazepam slows P3 processing selectively (Ray et al. 1992). Less surprising is the finding that schizophrenics with varied cognitive (and other) problems, possibly with cerebral atrophy, display impaired synthesis, release and uptake of glutamate and GABA in various parts of the CNS (Sherman et al. 1991; Simpson et al. 1992).

Conclusions

ERP subtraction waves (e.g. MMN, PN, Nd) are helping to inform on the nature and on the locus in time and space of the mechanisms that go to make up the series of operations we call attention. The judicious study of psychopathology and psychopharmacology is starting to show which anatomical systems (pathways and transmitters) may be involved in which processes. But perhaps still at the youngest stage of development is the knowledge that operational measures in one test reflect similar functions in another. Attentional processing is widely distributed but the mechanisms are localised: transmitter systems modulate and mediate, where the degree to which any one is involved is dependent on the situational demands. The further study of schizophrenic patients should help to improve this understanding (e.g. on impaired fronto-temporal cross-talk); it is to be hoped that they too will eventually benefit from this improvement.

Acknowledgments

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