Studies of Autonomic Psychophysiology and Attention in Schizophrenia

by Theodore P. Zahn

Abstract

Research from this laboratory over the years has found a rather consistent pattern of high baseline levels of many (but not all) indices of autonomic activity, slow adaptation, and attenuated autonomic reactivity to significant stimuli and situations in schizophrenia and that this pattern may be related to prognosis. Our studies have also shown that qualitatively similar changes occur in healthy subjects after a dose of dextroamphetamine and that certain aspects of the pattern are exaggerated in schizophrenic patients with cortical atrophy. It is hypothesized that there are specific autonomic markers for the two syndromes of schizophrenia defined by positive and negative symptoms which reflect distinct biological mechanisms. Current research seeks to determine the biological and symptomatic correlates of autonomic activity, to establish the specificity of certain autonomic markers to schizophrenia versus other major diagnoses, and to study the mechanisms and improve the assessment of attentional deficits in schizophrenia.

Studies of autonomic nervous system (ANS) activity by peripheral measures such as electrodermal activity (EDA), heart rate (HR), and vascular activity have a long history in schizophrenia research. These techniques have a number of advantages as research tools not possessed, in toto, by most other neurobiological methods. First, measurement is continuous and signal averaging is unnecessary in most cases so that it is possible to study such phenomena as physiological reactions and habituation to novel stimuli and situations, as well as the response to changes in cognitive and interpersonal demands. Second, the methods are noninvasive, well tolerated by subjects, and can be repeated frequently so that treatment effects and clinical changes can be studied. Third, many protocols demand minimal participation of the subject so that meaningful data can be obtained from patients who are quite psychotic and/or withdrawn.

In previous research using these methods, acute unmedicated patients exhibited a pattern of high baseline levels of EDA and cardiovascular activity, slow rates of adaptation to new situations and novel stimuli, and attenuated ANS reactivity to task performance and task-related stimuli compared to controls (Zahn et al. 1981a), similar to my earlier findings (Zahn 1975). We also showed that the ANS pattern described above predicted poor outcome on a 3-month followup.

Subsequently, we compared a more heterogeneous sample of schizophrenic patients (n = 60), free of medication for at least 2 weeks, with normal volunteers (n = 96) in a two-session protocol that included rest periods, a series of innocuous tones to elicit “orienting” responses (ORs), and two tasks—two-flash discrimination and tachistoscopic recognition. The results confirmed most of the findings in our previous studies—high baseline levels of ANS activity, slow adaptation, and attenuated response to tasks in schizophrenia (Zahn et al. 1985). However, two paradoxical findings may limit the generality of these conclusions. One paradoxical finding—as skin conductance level—was not higher in the
patients, replicating a finding of Zahn et al. (1981a), and smaller
related EDA in the schizophrenia subjects was observed under
most, but not all conditions. This is consistent with literature
reviews (Zahn 1986; Zahn et al., in preparation) showing more agree-
ment for a schizophrenic deficit in tonic increases in ANS activity to
task performance than for a deficit in phasic EDA elicited by signal
stimuli.

One reason for testing a large number of patients in a given pro-
tocol is to study individual differences among patients. In the study
just described, we examined the ANS data in relation to two other
biological markers. First, patients with an increase, no change, or a
decrease in psychosis ratings after a dextroamphetamine infusion
(done with Daniel van Kammen) did not differ in ANS activity in any
appreciable way. However, when eight patients with significant
cortical atrophy (CA) were compared to patients without signif-
ificant brain abnormalities (n = 20), the CA group had markedly and significantly smaller
electrodermal ORs to nonsignal stimuli, small and sluggish ANS
reactions to task performance, and a trend for high resting HR. The
CA patients were more deviant from normals than the control
patients in all these respects (Zahn et al. 1982).

Large samples also permit powerful multivariate analyses of the
data. We have fruitfully applied confirmatory factor analysis to the
controls’ data on this protocol (Zahn et al. 1986) to establish reliable
measurement models of several constructs of ANS activity, and we plan to do similar analyses
on the patients’ data to see if it has the same structure and to
simplify other analyses.

We observed many schizophrenia-like attributes of
ANS activity in normal men after single doses of dextroamphetamine
compared to placebo (Zahn et al. 1981b). These included increased
indices of arousal, slow habituation, reduced ANS reactivity to signal
stimuli, and reduced tonic response to task performance. Similar find-
ings have been reported for L-dopa effects on EDA (Horvath and
Meares 1974). This pattern is similar to the one seen in our previous
studies on unmedicated symptomatic schizophrenic patients, particularly those with a poor
short-term outcome, and is also similar to other reports of ANS
studies on newly admitted patients (Zahn 1986). These findings lend
credence to the hypothesis that this pattern is a state marker for a
dopamine psychosis and may be associated with the positive sympto-
mats in schizophrenia. Another marker—a failure of novel stimuli
to elicit autonomic ORs—has been observed in a relatively high propor-
tion of schizophrenics in many studies (Bernstein et al. 1982), sug-
gestng a profound dis turbance in involuntary attention. There is
some evidence that this nonre-
sponding occurs more frequently in chronic patients and may be asso-
ciated with negative symptoms or an absence of positive symptoms.
These two types of markers thus fit reasonably well with current
thinking about the phenomenology of schizophrenia, which contrasts the positive or florid symptoms of
schizophrenia, attributed to a dys-
regulation of dopamine, with the negative or defect symptoms of
nuclear schizophrenia, possibly accompanied by a structural brain
abnormality (Crow 1980).

We should be able to test the
hypothesis of specific ANS markers for the different syndromes of
schizophrenia by correlating our
data with behavioral ratings, biogenic amines, and their metabolites
in plasma and cerebrospinal fluid, and various brain scans. However
this turns out, being able to relate individual differences in structural
and functional properties of the
brain to well-confirmed ANS con-
comitants of schizophrenia is an
exciting prospect. Our preliminary
findings associating autonomic
hyporeactivity with cortical atrophy
are promising. However, since the
ORs of the subjects with CA were
not absent but just markedly
attenuated, this abnormality cannot
explain electrodermal nonrespond-
ing completely. A review of the
evidence is beyond the scope of this
short summary, but some speculations about relevant areas of the
brain are possible. For example, the “indifference reactions” and
“neglect” associated with right
parietal dysfunction might implicate this area in nonresponding.
Evidence for both excitatory (amyg-
dala) and inhibitory (hippocampus)
limbic influences on the electro-
dermal OR in monkeys exists. We
might also expect abnormal activity
in some of the areas that have
been associated with arousal such
as the brainstem reticular formation and the corpus striatum,
although the presumed excitatory
and inhibitory centers are so close
together that they might not be
separable with the current gener-
tation of scanners. One brain dys-
function that has been firmly
linked with schizophrenia—
hypoaactivity of the frontal cortex—
we might expect to be correlated
with attenuated task responsive-
ness, particularly a deficit in antici-
patory responding which we have
observed in several studies and feel
may index poor preparation to respond.

Our current protocol has been designed to assess a pattern of ANS activity across a variety of conditions. These include rest periods, an OR paradigm, and two simple reaction time (RT) tasks. We have several objectives besides the correlational studies mentioned above. One is to test the specificity of our ANS markers to schizophrenia. To this end, we have tested subjects with major affective disorder, obsessive-compulsive disorder, and panic disorder using part of the same protocol. We recently compared high-functioning autistic men with matched schizophrenic and control groups on part of this protocol (Zahn et al. 1987). The autistic subjects showed a similar deficit in responsivity under task conditions as the schizophrenics, but had normal ORs and showed different patterns of resting arousal indices and EDA laterality than the schizophrenic men. Another objective is to study in detail the ANS accompaniments of a classical RT paradigm (Rodnick and Shakow 1940) in order to assess their role in impairments of attention. Our previous research has established that schizophrenic patients typically have low elicited EDA and impaired anticipatory HR slowing in a simple warned RT task with constant foreperiods, supporting the hypothesis that slow RT in schizophrenia is due in part to impaired preparation to respond. The current study will look for ANS differences between constant and variable foreperiods to see if other frequently observed schizophrenic patterns such as disproportionate slowing of RT following long constant foreperiods (“crossover”) or short variable foreperiods are similarly amenable to a physiological interpretation.

Our current work involves departing from a longstanding avoidance of testing patients on standard neuroleptic (and anticholinergic) medication. One reason for this is to try to discover the sources of the variations among studies on ANS markers of schizophrenia. The absence of ORs mentioned earlier tends to occur in chronic medicated patients, while indices of high sympathetic arousal and slow habituation tend to occur in acute or episodic patients, frequently unmedicated. Although medication by itself clearly cannot account for all the conflicting results (Bernstein et al. 1982; Zahn 1986), it may interact with clinical variables. If nonresponding is a manifestation of a defect state in schizophrenia then it may not be affected by neuroleptic medication. The other parameters, which may be related to positive symptoms, should be affected by drugs. It is this sort of hypothesis that we hope to test in our current studies.

Finally, our current protocol includes choice and cross-modal RT procedures in order to study such phenomena as auditory versus visual sensory dominance, intersensory facilitation, and shifts in attention in schizophrenia, and to compare the similarity and efficacy of various previously established indices of attentional impairment.

References


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