

REPORT DOCUMENTATION PAGE

AD-A201 595

OTIC
ECTE
1 2 3 1988
LE

D

1b. RESTRICTIVE MARKINGS

3. DISTRIBUTION/AVAILABILITY OF REPORT
Approved for public release;
distribution unlimited.

4. PERFORMING ORGANIZATION REPORT NUMBER(S)
H 80

5. MONITORING ORGANIZATION REPORT NUMBER(S)
ARO 21733.4-LS

6a. NAME OF PERFORMING ORGANIZATION
University of Delaware

6b. OFFICE SYMBOL
(if applicable)

7a. NAME OF MONITORING ORGANIZATION
U. S. Army Research Office

6c. ADDRESS (City, State, and ZIP Code)
Newark, DE 19716

7b. ADDRESS (City, State, and ZIP Code)
P. O. Box 12211
Research Triangle Park, NC 27709-2211

8a. NAME OF FUNDING / SPONSORING ORGANIZATION
U. S. Army Research Office

8b. OFFICE SYMBOL
(if applicable)

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
DAAG-29-85-K-0085

8c. ADDRESS (City, State, and ZIP Code)
P. O. Box 12211
Research Triangle Park, NC 27709-2211

10. SOURCE OF FUNDING NUMBERS
PROGRAM ELEMENT NO. PROJECT NO. TASK NO. WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
Brain Mechanisms Underlying Individual Differences in Reaction to Stress: An Animal Model
(contract No. DAAG 29-85-K-0085)

12. PERSONAL AUTHOR(S)
Drs. Jerome Siegel and David F. Sisson

13a. TYPE OF REPORT
Final

13b. TIME COVERED
FROM 5/1/85 TO 8/31/88

14. DATE OF REPORT (Year, Month, Day)
October 29, 1988

15. PAGE COUNT
12

16. SUPPLEMENTARY NOTATION
The view, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

| 17. COSATI CODES | | |
|------------------|-------|-----------|
| FIELD | GROUP | SUB-GROUP |
| | | |
| | | |
| | | |

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
Visual Evoked Potentials, Augmenting-Reducing, Individual Differences

19. ABSTRACT (Continue on reverse if necessary and identify by block number)
The cat and rat were investigated as animal models of augmenting-reducing and its correlations with personality and behavior. It was determined that rats in a moderate anesthetic state induced by chloral hydrate and as identified by EEG spectral power distribution, exhibited VEPs qualitatively very similar to those recorded from awake, behaving preparations. It was also determined that variables relating to sensitivity to chloral hydrate were dependent upon the strain of rat while variables relating to VEPs were dependent upon pigmentation.

Stable, acute preparations enabled current-source density to be calculated in rats for VEPs evoked by light flash and electrical shock at the optic chiasm. The early components of these two types of VEP were found to have similar waveforms and were generated in the same cortical lamina, indicating that the same cortical circuitry is responsible for both types of VEP. (continued on reverse side)

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT
 UNCLASSIFIED/UNLIMITED SAME AS RPT. DTIC USERS

21. ABSTRACT SECURITY CLASSIFICATION
Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL

22b. TELEPHONE (Include Area Code)

22c. OFFICE SYMBOL

19. ABSTRACT (continued)

The VEP in cats was found to be an identifiable individual signature, stable over periods of more than one year. The VEP in response to an intensity series of light flashes at a medium range of intensities was reliable over time and showed significant individual differences in response to the more intense flashes. Some cats showed increasing VEP amplitudes to intense flash stimulation (augmenters), while others showed cortical inhibition, reducing the amplitude of the VEP to these intense stimuli (reducers). Augmenter cats were more exploratory and active in a behavioral chamber, and when confronted with a variety of novel and/or aversive stimuli were more reactive and responsive. This behavioral difference predicted task performance in an operant conditioning chamber. The augmenter cats were more reactive and were not as effective in exerting inhibitory control on behavior as were the reducers. Reducer cats learned a bar press inhibitory task more quickly, were less distracted by loud noise bursts and were able to tolerate more difficult tasks than the augmenter cats.

Pilot studies have been conducted in cats to determine which subcortical structures have modulating influences on the cortical VEP and thus are responsible for the augmenting-reducing differences between cats as well as the correlated behavioral traits. Electrical stimulation of basal forebrain, raphe dorsalis, superior colliculus and locus coeruleus just prior to flash VEP recordings indicate that raphe and colliculus have modulatory influences on visual cortex. The influence of raphe dorsalis is excitatory and increases with increasing flash intensity; the influence of superior colliculus is inhibitory and is constant over a range of flash intensities.

| | |
|--------------------|-------------------------------------|
| Accession For | |
| NTIS GRA&I | <input checked="" type="checkbox"/> |
| DTIC TAB | <input type="checkbox"/> |
| Unannounced | <input type="checkbox"/> |
| Justification | |
| By | |
| Distribution/ | |
| Availability Codes | |
| Dist | Avail and/or Special |
| A-1 | |

QUALITY
INSPECTED
2

BRAIN MECHANISMS UNDERLYING INDIVIDUAL DIFFERENCES
IN REACTION TO STRESS: AN ANIMAL MODEL

FINAL REPORT

DRS. JEROME SIEGEL, PATRICIA M. SAXTON and DAVID F. SISSON

OCTOBER 27, 1988

U. S. ARMY RESEARCH OFFICE

DAAG29-85-K-0085

UNIVERSITY OF DELAWARE
NEWARK, DE 19716

APPROVED FOR PUBLIC RELEASE;
DISTRIBUTION UNLIMITED

88 1122 082

THE VIEW, OPINIONS, AND/OR FINDINGS CONTAINED IN THIS REPORT ARE THOSE OF THE AUTHORS AND SHOULD NOT BE CONSTRUED AS AN OFFICIAL DEPARTMENT OF THE ARMY POSITION, POLICY, OR DECISION, UNLESS SO DESIGNATED BY OTHER DOCUMENTATION.

STATEMENT OF PROBLEM

In human studies, the changes in amplitude of the visual evoked potential (VEP) in response to changes in light flash intensity show individual differences which are very stable over short periods and moderately stable over longer periods (Buchsbaum, 1971; Birchall & Claridge, 1979; Soskis & Shagass, 1974). Those individuals whose VEP intensity-response curves describe a monotonic, increasing function are called augmenters, while those whose intensity-response curves describe a non-monotonic function that initially increases but decreases at higher light intensities are called reducers. Augmenting-reducing has been found to be correlated with clinical psychopathology (Buchsbaum, *et al.*, 1971; Schooler, *et al.*, 1976; Gershon & Buchsbaum, 1977; Buchsbaum, *et al.*, 1977), personality scales of extraversion-introversion (Haier, 1984) and sensation seeking (Zuckerman, *et al.*, 1974, 1980; Lukas 1981a), and with pain tolerance (Buchsbaum, 1978; Buchsbaum & Haier, 1983). It has also been demonstrated in other sensory modalities such as audition (Lukas & Mullins, 1983; Bruneau, *et al.*, 1986; Zuckerman, *et al.*, 1987). This readily obtained psychophysiological index may provide a measure of individual differences in response to high levels of sensory stimulation which would be valuable in screening personnel for performance during stressful task assignments. However, there is controversy concerning the links between augmenting-reducing and personality which stems for the most part from the correlative nature of these links (Lukas, 1981b; Connolly & Gruzelier, 1982; Raine, *et al.*, 1981; Soakis & Shagass, 1974; Andress & Church, 1980).

Information gained from the above behavioral studies offers some insight into mechanisms. The correlation between a strictly sensory phenomenon such as augmenting-reducing and a higher level brain function such as personality implies that both stem from a common modulatory influence on the cerebral cortex. The cortical areas known to process sensory information from different modalities are highly segregated; these areas are, in turn, highly segregated from cortical areas implicated in the expression of personality. The common modulatory influence is most likely a subcortical pathway that projects diffusely to all of cortex.

There are several known pathways that project diffusely to cortex. These can be grouped into two major categories. First, are the major transmitter pathways, *vis.* noradrenergic from locus coeruleus, dopamine from ventral tegmentum, cholinergic from basal forebrain, and serotonergic from dorsal raphe. Second are the non-specific thalamic sensory pathways *e.g.* pathways from the intralaminar nuclei.

To get away from correlative links, experiments designed to explore the mechanisms behind augmenting-reducing must be used.

The invasive nature of such experiments requires that an animal model of augmenting-reducing be developed. Previous studies with cats (Hall, et al., 1970; Lukas & Siegel, 1977) indicate that they can be divided into augmenters and reducers, that these divisions are reliable over periods of time up to at least a year (Saxton, et al., 1987a) and that these groups show correlated personality differences analogous to those observed in human augmenters and reducers (Saxton, et al., 1987b). Similarly, rats can be divided into augmenters and reducers -- also with correlated behavioral differences (Como, et al., 1979; Joseph, et al., 1981). Difficulties in using rats stem from much larger variability in VEPs than is seen in either humans or cats (unreported observations from our lab).

The research described in this final report is designed to expand the animal model for augmenting-reducing in rats and cats. Much effort has been put into developing an acute preparation in which VEPs are minimally different from chronic, behaving animals and VEP variability is maintained at a manageable level. A two-pronged effort is used to determine the neural mechanisms underlying augmenting-reducing. First, laminar and current-source density analyses of visual cortex are being used to determine the laminar origins of the components of VEPs. With this information, anatomical and physiological knowledge of visual cortex can be used to narrow down the putative mediators for this phenomenon. Second, determination of the effect of electrical and chemical lesions and electrical stimulation of subcortical nuclei on VEPs can be used to attempt to experimentally control the mechanisms that produce augmenting-reducing.

layers of visual cortex; physiology;
receptor, visual cortex, subcortical (EEG);
anatomy, physiology, psychological effects (??)

SUMMARY OF RESULTS

Our work during this contract period was divided between examining cats and rats as animal models for augmenting-reducing. In Wistar rats we used on-line EEG power spectrum analysis as a tool to identify and control the state of an animal, a major source of variability in evoked potential (EP) data, permitting us to maintain an animal in a stable, moderately anesthetized state during which VEP's were qualitatively comparable to those seen in the unanesthetized animal (Sisson, *et al.*, 1987, Sisson & Siegel, 1988). Anesthesia level in acute preparations was varied by i.v. injections of chloral hydrate, and the EEG and light-flash VEP's were recorded from visual cortex. Under deep anesthesia, EEG activity was concentrated in the 0.1 hz to 4 hz band with very little contribution from frequencies higher than 10 hz. After this period of deep anesthesia, EEG frequency distribution changed with peak power measured in the 4 - 8 hz range with a small increase in power in the frequency band between 11 and 30 hz. This moderate anesthetic state persisted for about 30 min. Two distinct forms of VEP's were highly correlated with these EEG frequency distributions. VEP's associated with the moderate anesthetic state were comparable to those reported from awake, chronic preparations. In VEP's associated with deep anesthesia, negative components were greatly attenuated or entirely absent; amplitudes of the positive components were increased as were the latencies of all components.

To ascertain whether these effects would be the same across different strains of rat, we repeated this experiment using albino and hooded Long-Evans rats (Sisson, *et al.*, 1988). Significant strain differences (Wistar vs. Long-Evans) were seen in the amount of chloral hydrate necessary to induce a deep state of anesthesia and in the duration of the deep state: Long-Evans rats were less sensitive to chloral hydrate. Significant differences between VEPs of pigmented and albino rats were observed, specifically in the latencies to peak of the VEP components (pigmented rats had shorter latencies).

With the ability to maintain a stable level of anesthesia in rats using chloral hydrate, we looked at the laminar organization of rat VEPs. Average visual evoked potentials (VEP's) from primary visual cortex, generated by light flash (fVEP's) or optic nerve electrical shock (eVEP's), were compared in acute rats. Waveforms of both types of VEP were similar for the first three (early) components (P_1 , N_1 and P_2); latency difference was about 25 msec. The later components of the two VEP's were different in shape and latency.

Current source density analysis was used to further compare the early components of fVEP's and eVEP's, again with similar

results. Current sinks with latencies coinciding with P_1 were distributed in layer IV and superficial layer V; their sources were found in layer I, superficial layer II and layer VI. Sinks with latencies coinciding with N_1 appeared in layer II/III and along the layer V-VI border; sources were located in layer IV. Sinks with latencies coinciding with P_2 were located in layers I and VI; sources were found in layers II and V. Therefore, the initial components of fVEP's and eVEP's appeared to be generated by the same cortical circuitry. Later components differed suggesting that the temporal characteristics of the underlying neuronal activity was important for their expression.

In cats, the N_1 and P_1-N_1 amplitudes slopes of the VEP at a medium or high range of flash intensities were characteristic of the individual cat (Saxton, *et al.*, 1987a). The N_1 slope at the medium range of intensities was a reliable measure as indicated by the finding that the slope of the averaged N_1 amplitude vs. flash intensity for three different sessions, ten months apart was highly correlated ($r > 0.9$). The slopes of these curves were correlated with spontaneous behaviors and with learning and performance measures during a bar pressing task for food reward (Saxton, *et al.*, 1987b). Cats who were relative augmenters at the high range of intensities were more active, exploratory and learned to bar press more quickly and efficiently. Reducers with a lower inhibitory threshold learned the differential reinforcement of low rate of response task more quickly, performed more efficiently, and were less disturbed by the introduction of loud noise bursts. Apparently, reducers had an active neural inhibitory process which was reflected in both their VEP slopes and in certain behavioral tasks.

We have also been looking at the effects of electrical stimulation of subcortical sites on cortical augmenting-reducing functions. Six cats have been examined so far, and basal forebrain, raphe dorsalis, superior colliculus and locus coeruleus have been stimulated. Preliminary results indicate that a conditioning stimulus train delivered to superior colliculus prior to a light flash has an inhibitory effect on ipsilateral P_1-N_1 and both ipsi- and contralateral N_1-P_2 , but that the magnitude of this effect is not different as a function of light flash intensity. A conditioning train delivered to raphe dorsalis produced an excitatory effect on ipsi- and contralateral N_1-P_2 , and this effect is intensity dependent in that the excitatory effect is greater with higher flash intensities.

PUBLICATIONS

- Curtis, M.M., Saxton (Wixom), P.M. and Siegel, J. Serotonergic influences in the amygdala affect behavioral inhibition in rats. *Soc. for Neurosci. Abstr.*, 14: in press, 1988.
- Curtis, M.M., Saxton, P.M. and Siegel, J. Effects of neuroactive agents administered intracerebrally on behavioral inhibition in cats. *Soc. for Neurosci. Abstr.*, 13:1714, 1987.
- Saxton, P.M., Siegel, J. and Lukas, J.H. Visual evoked potential augmenting/reducing slopes in cats -- 1. Reliability as a function of flash intensity range. *Person. individ. Diff.*, 8:499-509, 1987a.
- Saxton, P.M., Siegel, J. and Lukas, J.H. Visual evoked potential augmenting/reducing slopes in cats -- 2. Correlations with behavior. *Person. individ. Diff.*, 8:511-519, 1987b.
- Siegel J., Saxton, P.M. and Lukas, J.H. Cortical inhibitory processes and behavioral inhibition in cats. *IBRO Second World Congress on Neurosci.*, 1987.
- Sisson, D.F. and Siegel, J. Chloral hydrate anesthesia: EEG power spectrum analysis and effects on VEPs in the rat. *Neurotoxicol. Teratol.*, in press, 1988.
- Sisson, D.F., Siegel, J. and Westenberg, I.S. Depth of chloral hydrate anesthesia as a function of pigmentation and strain differences in rats. *Soc. for Neurosci. Abstr.*, 14: in press, 1988.
- Sisson, D.F., Siegel, J. and Lukas, J.H. Visual evoked potentials and EEG activity under different levels of anesthesia in rat. *Soc. for Neurosci. Abstr.*, 13:632, 1987.

PARTICIPATING SCIENTIFIC PERSONNEL

Dr. Jerome Siegel, Principal Investigator
Dr. Patricia Saxton, Associate Scientist
Dr. David F. Sisson, Associate Scientist
Marlene M. Curtis, Graduate Research Assistant
John Pujals, Undergraduate Research Assistant (B.A. - Biology)
James Doherty, Undergraduate Fellow
Brad Cox, Undergraduate Research Assistant
Eric Rubinson, Undergraduate Science and Engineering Fellow
David Gallatin Undergraduate Science and Engineering Fellow

BIBLIOGRAPHY

- Andress, D.L. and Church, M.W. Differences in brainstem auditory evoked responses between introverts and extroverts as a function of stimulus intensity. *Soc. for Psychophysiol. Research Abstracts, Psychophysiology*, **18**:156, 1980.
- Birchall, P.M.A. and Claridge, G.S. Augmenting-reducing of the visual evoked response as a function of changes in skin conductance level. *Psychophysiol.*, **16**:482-490, 1979.
- Bruneau, N., Barthelemy, C., Jouve, J. and Lelord, G. Frontal auditory-evoked potential augmenting-reducing and urinary homovanillic acid. *Neuropsychobiology*, **16**:78-84, 1986.
- Buchsbaum, M.S. Neurophysiological studies of reduction and augmentation. In Petrie, A. (Ed.), *Individuality in Pain and Suffering* (2nd Edition), University of Chicago Press, Chicago, IL, 1978.
- Buchsbaum, M.S. and Haier, R.J. Individual differences in augmenting-reducing evoked potentials. In Gale, A. and Edwards, J.A. (Eds.), *Physiological Correlates of Human Behavior*, Vol. III, Academic Press, London, 1983.
- Buchsbaum, M.S., Goodwin, F., Murphy, D. and Borge, G. AER in affective disorders. *J. Am. Psychiatry*, **128**:51-57, 1971.
- Buchsbaum, M.S. and Pfefferbaum, A. Individual differences in stimulus intensity response. *Psychophysiol.*, **8**:600-611, 1971.
- Buchsbaum, M.S., Post, R.M. and Bunney, Jr., W.E. Average evoked responses in a rapidly cycling manic-depressive patient. *Biol. Psychiat.*, **12**:83-99, 1977.
- Como, P.G., Joseph, R., Fiducia, D., Siegel, J. and Lukas, J.H. Visually evoked potentials and after-discharge as a function of arousal and frontal lesion in rats. *Soc. for Neurosci. Abstr.*, **5**:202, 1979.
- Connolly, J.F. and Gruzelier, J.H. Amplitude and latency changes in the visual evoked potential to different stimulus intensities. *Psychophysiol.*, **19**:599-608, 1982.
- Dyer, R.S. and Annau, Z. Flash evoked potentials from rat superior colliculus. *Pharmacol. Biochem. Behav.*, **6**:453-459, 1977.

- Fleming, D.E. and Bigler, E.D. Relationship between photically evoked after-discharge occurrence and hippocampal EEG rhythms in restrained and unrestrained albino rats. *Physiol. Behav.*, **13**:757-761, 1974.
- Gershan, E.S. and Buchsbaum, M.S. A genetic study of average evoked response augmentation/reduction in affect disorders. In Shagass, C., Gershan, S. and Friedhoff, A.J. (Eds.), *Psychopathology and Brain Dysfunction*, Raven Press, N.Y., 1977.
- Haier, R.J., Robinson, D.L., Braden, W. and Williams, D. Evoked potential augmenting-reducing and personality differences. *Person. individ. Diff.*, **5**:293-301, 1984.
- Hall, R.A., Rappaport, M., Hopkins, H.K., Griffin, R. and Silverman, J. Evoked response and behavior in cats. *Science*, **170**:988-1000.
- Joseph, R., Forrest, N.M., Fiducia, D., Como, P. and Siegel, J. Electrophysiology and behavioral correlates of arousal. *Physiol. Psychol.*, **9**:90-95, 1981.
- Lukas, J.H. Human augmenting-reducing and sensation seeking. *Soc. for Psychophysiol. Research Abstracts, Psychophysiol.*, **19**:333-334, 1981a.
- Lukas, J.H. Human visual evoked potential augmenting-reducing at the occiput and vertex. *Soc. for Neurosci. Abstr.*, **7**:450, 1981b.
- Lukas, J.H. and Mullins, L.F. Auditory augmenters are sensation seekers and perform better under high work loads. *Psychophysiol. (Abstr.)*, **22**:580-581, 1985.
- Lukas, J.H. and Mullins, L.F. Auditory augmenting-reducing and sensation seeking. *Psychophysiol. (Abstr.)*, **20**:457, 1983.
- Lukas, J.H. and Siegel, J. Cortical mechanisms that augment or reduce evoked potentials in cats. *Science*, **198**:73-75, 1977.
- Mullins, L.F. and Lukas, J.H. Auditory augmenters are sensation seekers -- if they attend to the stimulus. *Psychophysiol. (Abstr.)*, **21**:589, 1984.
- Raine, A., Mitchell, D.A. and Venables, P.H. Cortical augmenting-reducing: modality specific? *Psychophysiol.*, **18**:700-708, 1981.
- Ray, O.S. and Barrett, R.J. Behavioral, pharmacological and biochemical analysis of genetic differences in rats. *Behav. Biol.*, **15**:391-417.

- Saxton, P.M., Siegel, J. and Lukas, J.H. Visual evoked potential augmenting/reducing slopes in cats -- 1. Reliability as a function of flash intensity range. *Person. individ. Diff.*, **8**:499-509, 1987a.
- Saxton, P.M., Siegel, J. and Lukas, J.H. Visual evoked potential augmenting/reducing slopes in cats -- 2. Correlations with behavior. *Person. individ. Diff.*, **8**:511-519, 1987b.
- Saxton, P.M. and Siegel, J. Visual evoked potentials to light flash in cats: Is a frontal sinus reference electrode truly indifferent. *Soc. for Neurosci. Abstr.*, **9**:1195, 1983.
- Saxton, P.M. and Siegel, J. Visual evoked potentials to light flash in cats: Is a frontal sinus reference electrode truly indifferent. *Electroencephalog. and clin. Neurophysiol.*, **55**:350-354, 1983.
- Saxton, P.M., Siegel, J. and Lukas, J.H. Stability of the visual evoked potential to intensity series of light flashes in cat. *Soc. for Neurosci. Abstr.*, **9**:1195, 1983.
- Schooler, C., Buchsbaum, M.S. and Carpenter, W.T. Evoked response and kinesthetic measures of augmenting/reducing in schizophrenics: Replications and extensions. *J. Nerv. Mental Dis.*, **163**:221-232.
- Schwartzbaum, J.S. Interrelationship among multiunit activity of the midbrain reticular formation and lateral geniculate nucleus, thalamocortical arousal, and behavior in rats. *J. Comp. Physiol.*, **89**:131-157, 1975.
- Sisson, D.F. and Siegel, J. Chloral hydrate anesthesia: EEG power spectrum analysis and effects on VEPs in the rat. *Neurotoxicol. Teratol.*, in press, 1988.
- Sisson, D.F., Siegel, J. and Westenberg, I.S. Depth of chloral hydrate anesthesia as a function of pigmentation and strain differences in rats. *Soc. for Neurosci. Abstr.*, **14**: in press, 1988.
- Sisson, D.F., Siegel, J. and Lukas, J.H. Visual evoked potentials and EEG activity under different levels of anesthesia in rat. *Soc. for Neurosci. Abstr.*, **13**:632, 1987.
- Soskis, D.A. and Shagass, C. Evoked potential tests of augmenting-reducing. *Psychophysiol.*, **11**:175-190, 1974.

Zuckerman, M., Buchsbaum, M.S. and Murphy, D.L. Sensation seeking and its biological correlates. *Psychol. Bull.*, **88**:187-214, 1980.

Zuckerman, M., Murtaugh, T. and Siegel, J. Sensation seeking and cortical augmenting-reducing. *Psychophysiol.*, **11**:535-542, 1974.

Zuckerman, M., Simons, R.F. and Como, P.G. Sensation seeking and stimulus intensity as modulators of cortical, cardiovascular, and electrodermal response: A cross modality study. *Person. individ. Diff.*, **9**:361-372, 1988.