speed for accuracy on the part of the introverts.

Before we generalize from these results, several limitations should be considered. (i) The relaxed condition allowed the subjects as much time as they required to complete the test. This is more generous than even normal "power" (untimed) instructions. (ii) The timed conditions were shorter than normally allowed on standard ability tests. (iii) The performance shift from relaxed to time stress is a relative shift (scores were standardized within condition); almost all subjects solved more problems in the power condition. In the timed conditions, however, the shift is absolute rather than relative; when treated with caffeine, introverts correctly answered fewer problems and extroverts more problems. (iv) Differences in performance in the relaxed condition could be a result of differences in arousal (our hypothesis) or represent different levels of involvement in the task. If introverts are assumed to be relatively more interested in intellectual problems, they might be expected to do better when allowed unlimited time. In the timed conditions, however, this explanation is less convincing. In the same testing session some subjects were administered placebo and others caffeine—a condition that diminishes the likelihood of differential susceptibility of introverts and extroverts to possible expectations of the experimenter.

Our effects are interactive ones and not main effects. Caffeine-induced stress neither raises nor lowers average performance but rather increases the performance for some individuals and decreases it for others. Similarly, across the two drug conditions, there was no net superiority for either introverts or extroverts. These findings suggest a paradigm for studying the effects on performance of stressors in conjunction with dimensions of personality. Specifically, this methodology overcomes many of the objections raised to previous studies of the curvilinear relationship between stress and performance (*5*).

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15. The correlations with number right (uncorrected) were −.28, −.13, and +.14.
16. The means before standardization were 37.3, 21.1, and 21.9 (S.D. = 8.6, 8.5, and 9.0) for the relaxed, placebo, and caffeine conditions, respectively.
17. Similar analyses were done with the neuroticism scale from the Eysenck Personality Inventory, but there were no significant effects.
18. A preliminary study with 60 subjects and 100 mg of caffeine had similar results. Introverts ($N = 18$) fell from +0.25 to −0.36 sigma units, while extroverts ($N = 11$) rose from +0.01 to +0.22. Ambiverts ($N = 31$) rose slightly from −0.2 to −0.16.
19. We thank J. Barry and L. Gourley for assistance in collecting the data for the pilot study and L. G. Humphreys, M. Humphreys, and two anonymous reviewers for helpful comments on an earlier draft of this paper.

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Two Functional Effects of Decreased Conductance EPSP's: Synaptic Augmentation and Increased Electrotonic Coupling

Abstract. *Three electronically coupled motor neurons, which mediate inking behavior in* Aplysia californica, *receive both increased and decreased conductance excitatory postsynaptic potentials (EPSP's). The increased conductance EPSP's reduce electrical coupling among the cells, whereas the decreased conductance EPSP's increase electrical coupling. The decreased conductance EPSP's also augment the action of a previously ineffective sensory input and this augmentation is enhanced by the increase in electrical coupling. Both effects combine to trigger a stereotypic behavioral response.*

Studies of vertebrate and invertebrate nerve cells indicate that different neurons receive and generate a variety of electrical and chemical synaptic actions. For example, excitatory chemical synaptic actions are usually mediated by an increased conductance to Na^+ and K^+ (*1*), but similar although slower synaptic excitation can be mediated by a decreased conductance to K^+ (*2*). Some insight into the functional role of the synaptic diversity of neurons can be gained by examining the synaptic actions of nerve cells in relation to behavior. We here compare the functional consequences of increased and decreased conductance synaptic excitation for three electrotonically coupled motor cells and the behavior which they mediate. We find that a synaptically activated increase in membrane conductance reduces electrotonic coupling [see also Spira and Bennett (*3*) and Kater (*4*)]. This synaptic input triggers a stereotypic inking response to a single strong, suprathreshold stimulus. The synaptically activated decrease in membrane conductance increases electrotonic coupling. In addition, it augments the action of a previously ineffective sensory input (*5*). Both effects combine to trigger inking in response to closely timed subthreshold stimuli.

In response to noxious stimuli, *Aplysia californica* exhibits an all-or-none stereotypic response in which copious amounts of dark purple ink are ejected from the mantle cavity (*6*). This response is mediated by three identified motor neurons located in the abdominal ganglion ($L14_A$, $L14_B$, and $L14_C$). The three motor neurons are silent, have a high resting potential (approximately −65 mv), and are electrotonically coupled to one another (see Fig. 2A). A single brief electrical stimulus to the connectives (nerve tracts that carry input to the abdominal ganglion from the head ganglia), or to peripheral nerves, produces similar synaptic responses in all three nerve

cells: a fast complex excitatory postsynaptic potential (EPSP) (approximately 0.1 to 0.5 second in duration), usually followed by a slow EPSP (approximately 10 seconds to 3 minutes in duration) (Fig. 1, A and B) (*7*). A further distinction in the two types of EPSP's is revealed by examining the effects of altering the membrane potential of the motor cells. As is to be expected for an increased conductance EPSP, whose reversal level is generally close to 0 mv (*8*), depolarizing the membrane potential reduces the amplitude of the fast EPSP. In contrast, depolarization increases the amplitude of the slow EPSP (Fig. 1A). Similarly, hyperpolarization increases the amplitude of the fast EPSP and decreases the amplitude of the slow EPSP. The slow EPSP inverts at approximately −70 mv (about 5 mv below resting potential), which is in the range of the K Nernst potential in *Aplysia* neurons (*9*). In addition, the fast EPSP is accompanied by an increase and the slow EPSP by a decrease in input conductance (Fig. 1, A and B). These results are consistent with the interpretation that the fast EPSP results from an increase in ionic conductance and that the slow EPSP results from a decrease in ionic conductance.

To determine whether the slow EPSP is due to an actual reduction of a resting conductance in the motor cells, or to a removal of tonically active inhibitory input to them, we bathed the ganglion in high-Mg^{2+} seawater (four times normal) in order to block a possible inhibitory synaptic input. Blocking the synaptic input does not depolarize the motor cells, thereby excluding disinhibition as a mechanism for the slow EPSP (*10*).

Since both the slow and fast EPSP's result in excitation, we explored the possibility that they might have different functional consequences for behavior. As is the case for other increased conductance EPSP's, those generated in the ink gland motor cells excite because they move the membrane potential toward threshold for spike generation. Because they shunt the membrane resistance, these EPSP's also decrease the amplitude of other increased conductance excitatory synaptic potentials. Thus the depolarization produced by two separate increased conductance EPSP's is equal to or less than the algebraic sum of the individual EPSP's. Decreased conductance EPSP's also excite by depolarizing the membrane. However, because they reduce the conductance of the membrane, decreased conductance EPSP's can augment concomitant excitatory synaptic actions. To investigate the augmenting effects of the slow EPSP on subsequent input to the ink gland motor cells, we examined its consequences for a subthreshold sensory input from the siphon (*11*). We first stimulated the siphon skin with a train of brief electrical pulses. A stimulus intensity was chosen that produced a subthreshold, complex EPSP in the ink gland motor cells (Fig. $1C_1$). We next delivered a train of electrical pulses to the connectives of sufficient intensity to produce the slow EPSP without causing the cells to discharge (Fig. $1C_2$). When we timed the siphon stimulus to coincide with the peak of the slow EPSP, the previously subthreshold input triggered an accelerating burst of action potentials in the motor cells, which in turn produced the release of ink from the

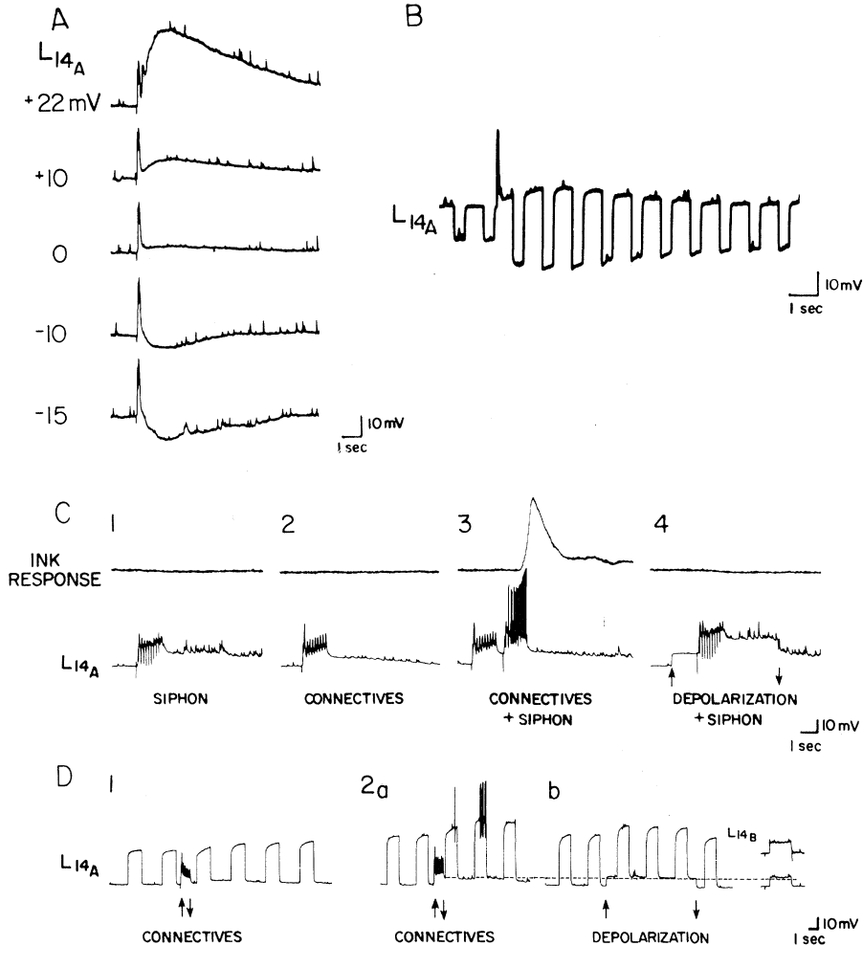

Fig. 1. (A) Effects of membrane potential on fast and slow EPSP's. In (A) and (B), EPSP's were produced by a single (1.5 msec) electrical pulse to the connectives. Numbers at left indicate displacement of membrane potential from resting level (0 mv). Depolarization reduces the amplitude of the fast EPSP and increases the slow EPSP. Hyperpolarization increases the fast EPSP and reduces the slow EPSP, inverting it at approximately −70 mv. (B) Resistance increase during slow EPSP. Repeated hyperpolarizing current pulses were injected from one intracellular electrode; membrane potential was recorded with a second independent electrode. (C) Synaptic augmentation of sensory input. The top trace is the photocell record of ink response; the bottom trace is the intracellular record from $L14_A$. (C_1) Siphon skin is electrically stimulated (1.5-msec pulses, six per second for 2 seconds), producing a subthreshold complex EPSP in $L14_A$. (C_2) Connectives are stimulated (1.5-msec pulses, six per second for 2 seconds) to produce a slow EPSP. (C_3) Following identical connective stimulation, the siphon stimulus is timed to coincide with the slow EPSP, which now triggers a burst of action potentials in $L14_A$, leading to the release of ink from the ink gland. (C_4) Depolarization comparable to that produced by the slow EPSP (C_2 and C_3) (produced by an independent intracellular electrode) superimposed on siphon input does not produce augmentation. (D) Synaptic augmentation of electrotonic pulses. In a separate experiment, constant current depolarizing pulses are repeatedly delivered. (D_1) Following connective stimulation (six per second for 1 second, at arrows), subthreshold pulses are augmented by the slow EPSP. (D_{2a}) Both the electrotonic pulse and connective stimulation were increased slightly from (D_1), so that the slow EPSP augments the pulse sufficiently to trigger a burst of spikes. The resulting augmentation is less than C_3, at least in part because the depolarizing pulse is much briefer than the synaptic action in C_3. (D_{2b}) Depolarization of $L14_A$ (produced by injecting current into $L14_B$ to ensure that both cells are depolarized; see inset at right), comparable to depolarization produced by the slow EPSP, does not produce augmentation (dashed lines are to facilitate comparison).

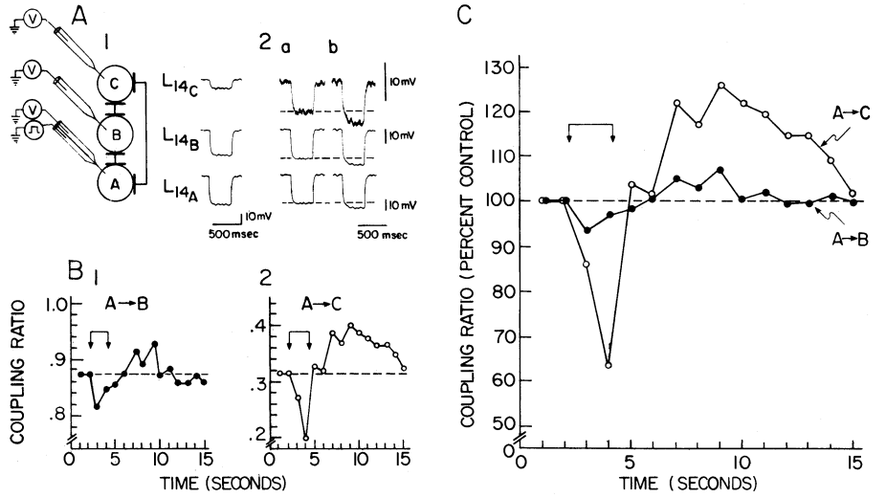

Fig. 2. (A) Increased electrotonic coupling during the slow EPSP. (A_1) Current was injected in $L14_A$ and membrane potential changes were recorded from all three cells (diagrammed at left). (A_{2a}) Gain in $L14_C$ and $L14_B$ was increased to match pulse amplitude to $L14_A$. (A_{2b}) During a slow EPSP, the electrotonic potentials in all three cells increased (due to increased input resistances), but the increase is relatively greater in $L14_B$ and especially in $L14_C$ than in $L14_A$, reflecting an increase in coupling (see text). (B) Decrease and increase in coupling during fast and slow EPSP's. Coupling was monitored with hyperpolarizing pulses (400 msec in duration, one per second). Connectives were stimulated (1.5-msec pulses, six per second for 2 seconds, indicated by arrows), producing a complex fast EPSP during the train and a slow EPSP following the train. (B_1) Coupling between $L14_A$ and $L14_B$; (B_2) coupling between $L14_A$ and $L14_C$. The decrease in coupling during the fast EPSP and increase during the slow EPSP are proportionately greater for weakly coupled $L14_C$. (C) Percentage change in coupling for $L14_A \rightarrow L14_C$ (open circles) and for $L14_A \rightarrow L14_B$ (closed circles). Control (100 percent) is the coupling ratio before stimulation.

purple gland (Fig. $1C_3$). This augmentation of the siphon input was not simply due to the depolarization produced by the slow EPSP. Comparable depolarization produced by intracellular current did not augment the same siphon input (Fig. $1C_4$).

Additional evidence that this augmentation involves a resistance increase in the postsynaptic cell is provided by the finding that depolarizing electrotonic potentials that are barely threshold for spike initiation are also augmented by the slow EPSP (Fig. 1D) (*12*). Although we cannot exclude presynaptic facilitation (*13*) as an additional mechanism, these experiments indicate that the postsynaptic resistance increase contributes importantly to the augmentation. This augmentation also cannot be accounted for by a nonlinearity in the current-voltage relationship of the ink gland motor neurons because it is linear in this range of membrane potential (*6*). Thus the slow EPSP provides a postsynaptic mechanism for heterosynaptic augmentation (*5*), as first predicted by Weight (*14*).

Since the motor cells are electrically coupled, it was of further interest to examine the modulating effect of the two types of EPSP's on electrotonic transmission. We therefore injected repeated hyperpolarizing constant current pulses into one of the motor cells while simultaneously recording from one or both of the others. During a 2-second train of fast EPSP's, the coupling ratio between the cells decreased (Fig. 2, B and C, pulses 3 to 5), as first described for a conductance increase inhibitory postsynaptic potential by Spira and Bennett (*3*). Therefore electrotonically connected cells can be uncoupled by excitatory increased conductance actions as well as by inhibitory increased conductance actions. During the slow EPSP, however, the coupling ratio between the cells increased (Fig. $2A_2$ and Fig. 2, B and C, pulses 6 to 15). Presumably the junctional resistance did not change and the coupling increased because the slow EPSP increased the input resistance of the postsynaptic cells.

The electrotonic coupling among the ink cells is not uniform: the coupling between $L14_A$ and $L14_B$ is usually greater than that between either cell and $L14_C$ (Fig. 2, A_1, B_1, and B_2). As might be predicted by the equivalent circuit for electrotonically connected cells (*15*), we found that the degree of modulation varied inversely with the effectiveness of coupling. Both the decreased coupling during the fast EPSP and the increased coupling during the slow EPSP are proportionately greater for the weakly coupled $L14_C$ than for the strongly coupled $L14_A$ or $L14_B$ (Fig. 2C). In the experiment of Fig. 2 the efficacy of electrotonic coupling between the cells was modulated across a twofold range (from a coupling ratio of 0.2 to 0.4, Fig. 2B). In different experiments the modulating action can range from 1.5- to 4-fold.

Thus during the slow EPSP, two main factors combine to enhance the response: (i) increase in synaptic potentials due to increased input resistance and (ii) increase in the electrotonic spread between cells when they are not uniformly depolarized either by the postsynaptic potentials or by subsequent spike activity.

Inking elicited by a brief noxious stimulus to the head or siphon is predominantly triggered by the fast, increased conductance EPSP (*6*). What then is the function of the slow EPSP? Our data suggest that the slow EPSP provides a second means of activating the inking system. If a single strong stimulus is not sufficient to produce inking, the slow EPSP ensures that inking will be triggered even by a considerably weaker stimulus if it follows the first stimulus within a few seconds. This idea is supported by recent behavioral experiments that indicate that all-or-none inking can indeed be produced in two ways: (i) by a suprathreshold stimulus to a single site or (ii) by two subthreshold stimuli (delivered to the same or to different sites), which can be separated in time by as much as 2 seconds, a period when the maximum depolarization produced by the first stimulus has passed (*6*). Thus the augmentation produced by the slow EPSP provides a novel mechanism for temporal and spatial summation of two subthreshold stimuli. In the case of the inking system, this can lead to the triggering of a stereotypic behavioral act.

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7. We have studied the decreased conductance EPSP in 22 experiments. In several other experiments, this EPSP was not initially observed, but could be revealed by varying one or more parameters of connective stimulation, such as pulse intensity, duration, or polarity. In a few cases, however, connective stimulation produced a slow depolarizing response that resembled the slow EPSP in its time course, but differed from it in being associated with a conductance increase. The source of this variability is not known. Most likely it is due to the fact that the connective is a mixed nerve and that several different inputs to the motor cells, with similar thresholds to electrical stimuli, are activated. Alternatively, variations in the resting K^+ conductance in the ink gland motor cells in different preparations might contribute to the variability of the decreased conductance EPSP.
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10. Increasing Mg^{2+} increased the input resistance by 30 to 50 percent in the ink gland motor cells, but this effect was not specific. The input resistance of nerve cells that do not receive the decreased conductance EPSP, such as the gill motor cell L7, was also increased by the same amount.
11. Animals were anesthetized by injection of isotonic $MgCl_2$ (25 to 50 percent of body weight) to prevent inking during dissection. The abdominal ganglion and the mantle (containing the ink gland) were excised and pinned in a recording chamber with a Sylgard floor. Seawater was perfused across the gland and channeled across the photocell to measure the inking response [for details, see (*6*)]. The siphon was stimulated by means of platinum wires sewn into the skin; the connectives were stimulated by means of Ag-AgCl electrodes built into the chamber.
12. Another factor that might contribute to the augmentation of the depolarizing pulse is the possibility that the decreased conductance EPSP may reduce the voltage threshold for spike initiation [for a discussion, see M. V. L. Bennett, B. Hille, S. Obara, *J. Neurophysiol.* **35**, 585 (1970)].
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15. The coupling coefficient from cell 1 to cell 2 (K_{12}) is given by $K_{12} = r_2/(r_2 + r_c)$, where r_2 is the input resistance of cell 2 and r_c is the junctional resistance. From this equation it follows that the greater r_c is in relation to r_2, the greater will be the enhancement of coupling due to a decreased conductance EPSP [see M. V. L. Bennett, *Ann. N.Y. Acad. Sci.* **137**, 509 (1966)].
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Lead Poisoning: Altered Urinary Catecholamine Metabolites as Indicators of Intoxication in Mice and Children

Abstract. *Whether neuropsychological impairment occurs in children with increased lead absorption who are without clinical symptoms is of current concern. This issue, which involves potentially large numbers of children, remains unresolved, in part because of the lack of sensitive biochemical indicators of the effects of lead on the nervous sytem. In experimental subclinical lead poisoning in mice, significant increases in homovanillic acid and vanillylmandelic acid have been found in brain and urine. In children with increased lead absorption, these acids were measured in urine collected quantitatively under controlled dietary conditions; preliminary results show fivefold increases in the daily output of these compounds. These data suggest that the altered catecholamine metabolism also occurs in children.*

Current screening programs have revealed many young children with increased lead absorption. While a high proportion of these children have biochemical evidence of impaired heme synthesis, few have clinical symptoms compatible with plumbism (*1*). It is unknown whether this subclinical degree of increased lead absorption causes either transitory or permanent impairment of the developing nervous system in the very young. Studies of children by standard psychometric and neurophysiological techniques have yielded conflicting results: some reports suggest that there is a statistically significant association between asymptomatic or mildly symptomatic increased lead absorption and subtle, but long-lasting, impairment in behavior and cognitive function (*2*), but other studies have not found lead-associated deficits (*3*). The role of lead in the causation of impaired nervous system function, in the absence of encephalopathy, is difficult to determine, in part because of the lack of sensitive neurochemical indicators of effects of lead on the nervous system (*4*). We report here initial data on the urinary output of two catecholamine metabolites, 4-hydroxy-3-methoxymandelic acid (vanillylmandelic acid, VMA), and 4-hydroxy-3-methoxyphenylacetic acid (homovanillic acid, HVA), in asymptomatic and mildly symptomatic young children with increased lead absorption and biochemical evidence of disturbed heme synthesis. The preliminary results strongly suggest that catecholamine metabolism is altered in such patients.

The clinical investigations were undertaken after studies on an animal model of subclinical lead poisoning. Animal models of childhood lead poisoning have demonstrated sequelae of impaired learning and hyperactivity (*5–7*). Associated with these disorders are significant alterations in behavioral response to several drugs, particularly an attenuation or, in lead-treated hyperkinetic mice, a reversal of amphetamine-induced stimulation of motor activity (*7–9*). Neurochemically, long-term postnatal exposure of rodents to lead produces enhanced noradrenergic function and inhibition of cholinergic function in the central nervous system (*9–11*).

The observation that in vivo lead exposure alters the function of at least one catecholamine neurotransmitter provided the rationale for investigating the usefulness of measuring the catecholamine metabolites HVA and VMA in the urine of lead-treated hyperkinetic mice and of children with increased lead absorption. In mice, brain levels of HVA and VMA were also measured.

Lead-exposed mice (CD-1, Charles River Laboratories) aged 40 to 70 days were used in these studies; methods of postnatal exposure of mice to lead acetate in drinking water (5 mg/ml) are described in (*5*). The mice used in these studies were exposed continuously from birth; no decreases in brain or body weights resulted from long-term lead treatment. Mice were housed individually in stainless steel metabolism cages for 24 hours for urine collections. The cages were washed with 0.01*N* HCl and these washes were combined with urine for assays. The urine and washes acidified to *p*H 2.0 and whole forebrains ob-

Table 1. Concentrations of HVA and VMA in whole brain and urine of control and lead-treated mice (males, 40 to 70 days of age). Values are means ± standard errors of the mean. Each determination was done in duplicate.

Metabolite	Concentration in brain (μg/g, wet weight)		Brain, lead/control (%)	Concentration in urine ($\mu g\ ml^{-1} day^{-1}$)		Urine, lead/control (%)
	Control	Lead		Control	Lead	
HVA	0.092 ± 0.008 (N = 12)	0.122 ± 0.013 (N = 9)	133*	6.510 ± 1.130 (N = 11)	17.292 ± 4.216 (N = 11)	265*
VMA	0.060 ± 0.001 (N = 6)	0.089 ± 0.009 (N = 6)	148*	6.829 ± 1.632 (N = 9)	14.782 ± 2.291 (N = 11)	216*

*$P < .05$.