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Contributions of Inhibitory Mechanisms to Unified Theory in Neuroscience and Psychology

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Findings from many areas of psychology and neuroscience indicate that inhibitory mechanisms may contribute to relationships between numerous causal variables and an equally diverse set of outcome variables. Outcome variables that implicate inhibition include measures from physiology, perception, attention, action, learning and episodic memory, semantic memory, emotion, and psychopathology. Inhibition-related causal variables include childhood development and aging, hypoxia and other brain insults, and socialization. If confirmed by further research, a theoretical framework with inhibition as one of its core mediating constructs has several strengths, including unified explanations for diverse relationships, mechanistic models for phenomena, insight into the principles that underlie observed relationships, and mechanistic translations of existing abstract, theoretical constructs.

Previous papers in this special issue have analyzed possible roles for inhibitory processes in specific areas relevant to neuropsychology (e.g., attention, aging). These papers have documented carefully the role of inhibition in the specified domains and have also identified associated limitations and weaknesses of inhibitory hypotheses. Indeed, several researchers were skeptical that existing phenomena had yet demonstrated a necessary role for inhibition in their area.

To complement these detailed analyses, I outline in general and undeniably speculative terms a unified framework for possible roles of inhibition across diverse areas of psychology and neuroscience. The basic hypothesis is that inhibitory mechanisms mediate in part the effects of head injury, aging, drugs, and a myriad of other causal variables on diverse physiological

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and behavioral consequences, such as seizures, attention, memory retrieval, and aggression.

Any such ''grand'' endeavor warrants a number of caveats. The first caveat is that I will necessarily be brief, stating my claims in a concise way and including just sufficient commentary and citations to demonstrate the plausibility of each claim. Plausibility is a more modest goal than trying to confirm that all claims are certain. Given this modest goal, space limitations, and the availability of more detailed examinations of the problems (e.g., other papers in this issue), I mention only briefly some of the negative findings and theoretical objections that could be aligned against the proposed relationships. The references provide a starting point for interested readers, many of whom already know enough about the areas to appreciate the complexity and uncertainty of the present suggestions.

A second caveat concerns my broad use of the term inhibition, by which I mean any mechanism that reduces or dampens neuronal, mental, or behavioral activity. This includes such molecular biochemical processes as the neuronal inhibition mediated by GABA and other inhibitory neurotransmitters, such intermediate-level cognitive processes as suppression of distractors in selective attention tasks, and such high-level executive processes as telling oneself to ''slow down.'' These different levels of description all involve suppression of one form or another. As a preliminary and simplifying assumption, the molecular and molar levels are assumed to be generally congruent, although not universally so (e.g., inhibition of inhibition has excitatory behavioral effects).

The danger is that defining inhibition so loosely may make the concept meaningless. Despite the wide range of phenomena incorporated under the general rubric of inhibition, however, the defining element in any suppression mechanism remains a diminuation of ''activity'' relative to that which would occur without suppression, and this core element transcends conceptual levels from the molecular to the molar. The hypothesized correspondence between various uses of the term inhibition can also be viewed as a tentative assumption, the validity of which will depend on whether it leads to simple, mechanistic explanations for observed phenomena. Consider the hypothesis that inhibition, broadly defined, strengthens during childhood and weakens during aging. This premise can accommodate multiple curvilinear relationships between age across the life-span and various biological and behavioral measures (e.g., the incidence of seizures, performance on selective attention tasks, susceptibility to interference in memory tasks), but only if the assumption is correct that inhibitory mechanisms in diverse neuronal and behavioral domains change in parallel as a function of age (or of such correlated variables as physiological deterioration and disease).

A third caveat is that the present emphasis on inhibition might wrongly lead to the interpretation that inhibition is the only factor operating in biological and psychological systems (i.e., that excitation plays a minor role) or

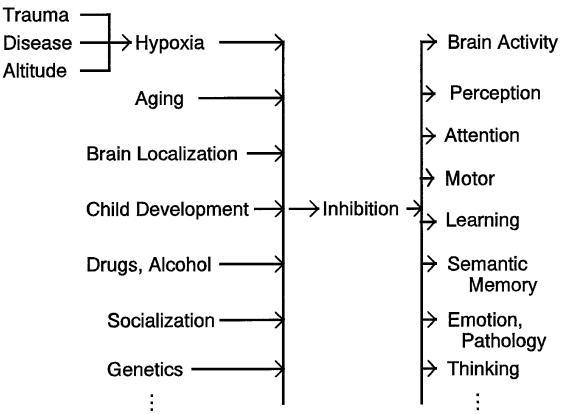

FIG. 1. Inhibition as a mediator between causal factors and behavior.

that the integrative effects of excitation and inhibition are simple ones. Such is not my intention, inasmuch as the important roles of excitatory processes are beyond challenge and inhibition itself is defined with respect to some background level of excitation. The complex integrative effects of excitation and inhibition are clearly demonstrated in early visual processes (Nicholls, Martin, & Wallace, 1992, Chapter 16), where light hyperpolarizes rods and leads to complex excitatory and inhibitory events involving richly interconnected horizontal, amacrine, bipolar, and ganglion cells. It even appears that single amacrine cells can both excite on-center ganglion cells and inhibit off-center ganglion cells (Nicholls et al., 1992).

Given such complexities, one concerned reviewer correctly commented that: ''In general, during enhancement (excitation) or suppression (inhibition) of any sensory or cognitive process, one is going to be able to find different levels at which biophysical measurements show that both inhibition and excitation are simultaneously occurring.'' This is a view with which I entirely agree. Rather than eliminate a role for excitation or minimize this integrative view, my goal is to identify suggestive evidence that common inhibitory mechanisms contribute to diverse biological and behavioral phenomena and, by emphasizing the explanatory contribution of those inhibitory mechanisms, to promote an interactive model in which inhibitory mechanisms are exploited as fully as excitatory processes in trying to achieve unified theories for human behavior.

OVERVIEW OF THE THEORETICAL FRAMEWORK

Figure 1 presents a unified theoretical framework in which inhibition is assigned a major role. The central construct of inhibition mediates in part the effects that the causal factors listed to the left have on the behavioral outcomes listed to the right. The right column lists diverse areas of psychol-

ogy and related disciplines in which there is evidence for a contribution by inhibitory mechanisms; these range from elementary biological processes (e.g., direct measures of brain function) to basic psychological processes (e.g., perception and attention) to complex psychological domains (e.g., emotion and psychopathology). The contribution of inhibitory mechanisms to these behaviors is represented by the diverging relations between the mediating construct of inhibition and the various behavioral domains.

An equally diverse set of factors that have been causally implicated in human behavior and experience appear to the left of inhibition. Such factors as hypoxia and other brain insults, brain localization, and childhood development and aging are hypothesized to affect inhibitory processing, as represented by the converging relations extending from the factors to the construct of inhibition.

This unifying framework, in which numerous causal factors influence inhibitory processes that contribute to diverse behaviors, can in principle predict and explain many cause–effect relationships for which inhibition acts as a unifying intervening variable. To illustrate, (a) some of the relation between head injury and attentional dysfunction could be explained by damage to inhibitory mechanisms resulting in a diminished capacity to suppress distractors; (b) a relation between aging and poor memory could be due in part to the weakening of inhibition with age and a lessened ability to inhibit interfering responses or associations; and (c) a relation between alcohol intoxication and aggression would follow from diminished inhibition and weakened restraints over impulsive and violent reactions to frustration. Many such relations are in principle consistent with models in which causes have their behavioral and neurological effects in part by virtue of intervening inhibitory mechanisms.

One benefit of this inhibitory framework is its potential to provide unified explanations that cut across quite diverse domains. Because inhibition is incorporated into models for attention, picture naming, aggression, and numerous other behaviors, causal factors that affect inhibition should reveal themselves by correlated changes in diverse inhibition-related behaviors. Dustman and his colleagues (this issue), for example, have demonstrated curvilinear relationships across the lifespan between age and various physiological and perceptual measures that implicate inhibitory processes. Additional examples of curvilinear relationships are described later. Such relationships can be explained parsimoniously by the unifying assumption of an increase in the relative strength of inhibition during childhood and a decrease in aging.

As a second benefit, a general framework that advocates important roles for inhibition promotes the development of mechanistic explanations for psychological phenomena. Mechanistic models explain behavior in terms of successive states of activation of mental representations or their neuronal equivalents, with transition from one state to another determined by excitatory

and inhibitory processes. When such models are well developed, knowledge of the inputs and the structure of the system are sufficient to explain the resulting behavior.

Inhibition permits the development of models for phenomena that may otherwise be difficult to account for in a mechanistic way. The contribution of inhibition seems particularly useful in modelling phenomena that involve suppression of a response except in certain contexts (e.g., feature positive and related Pavlovian conditioning paradigms) or selection from distracting or competing events (e.g., selective attention, inhibition of irrelevant labels in picture-naming tasks). Such phenomena can be difficult to explain mechanistically without incorporating both inhibitory and excitatory mechanisms, as illustrated by previous papers in this special issue. According to the proposed view, inhibition constitutes one of the fundamental building blocks with which to model human behavior and experience, analogous to the role that levers and their associated physical laws play in understanding the behavior of machines. Excitatory processes constitute another essential building block.

A third potential benefit of the inhibition model is that it can explain why certain cause-effect relationships are observed. That is, it can answer such fundamental questions as why inhibitory functioning increases during childhood and decreases in aging, producing the curvilinear relationships mentioned earlier. With respect to the decrease in inhibition with age, for example, I later describe evidence: (a) that aging is associated with various physiological changes that compromise delivery of oxygen to the brain (e.g., pulmonary conditions, cardiovascular disease, erythrocyte dysfunction) and (b) that compromised oxygenation of the brain (i.e., hypoxia) may impair inhibitory neurotransmitters and processes more than excitatory ones. Together these findings can explain a decline in inhibition with age, rather than leaving the observed relationship as a mere coincidence or accident of nature.

As a fourth benefit, the inhibition model provides a mechanistic basis for some current theories about the proposed relationships. Cognitive changes during childhood, for example, have been explained by such abstract Piagetian constructs as reversibility, centration, and inadequate perspective-taking skills. Because these Piagetian constructs all involve suppression (e.g., of an existing percept), inhibition could contribute to a mechanistic realization of the abstract, theoretical constructs proposed by Piaget. Similar concretization is possible for theoretical constructs in other domains to which the model has been applied.

The remainder of this paper expands briefly on the elements of the model and its anticipated benefits. The behavioral consequences of inhibition are examined first, followed by the various causal factors that affect inhibition. As readers might expect given the scope of the framework, and as noted earlier, coverage of the different areas will be brief and generally less critical than warranted.

TABLE 1
Inhibitory Effects

Measures of brain activity
Biochemical: GABA, serotonin, dopamine
Electrophysiology and imaging: VEPs to patterned/unpatterned stimuli (Dustman)
Seizures: Neurotransmitters (Lloyd), kindling-induced (Burnham), pyridoxine deficiency and bicuculline (Avoli; McCormick), progabide (Bartholini)
Perception
Physiology: Receptive field size and GABA antagonists (Hicks)
Behavior: Prepulse inhibition (Geyer)
Attention
Physiological: Visual cortex (Moran & Desimone)
Behavior: Negative priming (Tipper), network model for figure-ground (Kienker)
Motor
Physiological: Cerebellum (Eccles)
Behavior: Proximity effects (Kornblum), uncertainty (Jensen)
Learning and episodic memory
Conditioning: Summation and retardation tests (Williams)
Episodic memory: Interference, retrieval blocking: (Roediger & Neely)
Semantic memory
Semantic retrieval: Uncertainty (Clark; Lachman; Paivio), number facts (Campbell & Clark), interference from unrelated primes, TOT (Brown)
Word identification: Phonetic similarity (Goldinger)
Emotion, personality, and psychopathology
Aggression: Seizures (Mark & Ervin, Rosenzweig & Leiman), frustration (Berkowitz), GABA (Mandel)
Schizophrenia: Prepulse inhibition (Geyer), negative priming (Beech & Claridge)
Theories: Loosened associations (Meehl), frontal lobes

INHIBITORY MECHANISMS AND BEHAVIOR

Inhibition has been implicated in a wide range of behaviors from diverse areas of neuroscience and psychology, some of which are listed in Fig. 1 and Table 1. The behaviors are ordered roughly from molecular behaviors of a physiological sort to molar and complex behaviors that represent higher levels of human functioning.

Measures of Brain Activity

The present scheme identifies measures of brain activity as one way that inhibitory functions can be assessed or reflected in behavior. These measures often provide the most direct evidence for underlying inhibitory mechanisms.

Biochemical. Biochemical assays provide direct and rich data on inhibitory functioning in the brain, although the behavioral equivalency of levels of excitatory and inhibitory neurotransmitters is a complex issue and complications arise from neurotransmitters that are inhibitory or excitatory depending on location or context. GABA, a major inhibitory neurotransmitter in cortex (Roberts, 1987), is widely distributed throughout the brain (Cohen,

1988) with 20% of neurons in certain cortical areas being GABAergic (Nicholls et al., 1992). Houghton and Tipper (this issue) outline in some detail the important role of GABA in neural and psychological functioning. Other neurotransmitters that serve inhibitory functions include serotonin and dopamine (Cohen, 1988; Cooper, Bloom, & Roth, 1991; Rosenzweig & Leiman, 1989).

Although the functional importance of neurotransmitters cannot be equated with their amounts, the ubiquity of inhibitory neurotransmitters in the central nervous system is nonetheless consistent with the hypothesis that inhibition performs important behavioral functions, primarily by qualifying activity initiated by the equally important excitatory neurotransmitters. This claim is consistent with much behavioral evidence.

Electrophysiology and imaging measures. Dustman, Emmerson, and Shearer (1990) summarize various electrophysiological indicators of inhibitory functioning, several of which are also discussed by Dustman, Emmerson, and Shearer (this issue). As one example, activity levels for evoked potentials elicited by patterned stimuli have been correlated (across electrode sites) with activity levels for unpatterned stimuli. Because diminished inhibition reduces contrast between the elements of the patterned stimulus, relatively high correlations (i.e., high similarity in the brain's response to patterned and unpatterned stimuli) suggest low levels of lateral inhibition whereas low correlations suggest higher levels of lateral inhibition (see Dustman et al.'s paper in this issue and later discussion of child development and aging).

Simple measures of EGG activity may also permit inferences about inhibitory functioning, although the story is complex. Synchronized, large-amplitude, low frequency waves suggest weak inhibition, and desynchronized, low-amplitude, high frequency waves suggest strong inhibition (Roberts, 1987). This characterization is consistent with the basic nature of inhibition, inasmuch as high activity at one site would dampen activity at sites linked by inhibitory connections and promote activity at noninhibited sites linked by excitatory connections. Complicating the picture, however, diffuse inhibitory connections can actually facilitate synchronous firing of neurons given appropriately timed excitatory inputs (Engel, 1989, p. 55).

PET, MRI, and other imaging methods provide additional data relevant to inhibitory functioning but, again, inferences about inhibition are complex and may require functional knowledge about specific brain areas. Reduced brain activity cannot be interpreted simply as increased inhibition. As discussed later, for example, knowledge about frontal lobe functioning suggests that frontal hypoactivity probably reflects diminished rather than increased cortical inhibition. Increasingly precise techniques that permit imaging of specific neurotransmitters, such as the inhibitory transmitter GABA (Preece, Jackson, & Houseman, 1994), along with better developed psychological models, should redress some ambiguities inherent in current technologies.

Seizures. Susceptibility to seizures provides one natural indicator of the relative balance of excitation and inhibition and can be used to measure changes in the relative strength of inhibitory processes as a function of such causal factors as aging and head injury. A number of clinical and experimental models maintain that seizures can and often do result from diminished inhibition relative to excitation, as shown by evidence on neurotransmitter levels in both natural (Lloyd, Bossi, Morselli, Rougier, Loiseau, & Munari, 1985) and kindling-induced seizures (Burnham, 1989), and by experimental work on the chemical induction of seizures using pyridoxine deficiency or such GABA-antagonists as picrotoxin and bicucilline (Avoli, 1988; McCormick, 1989). The successful treatment of seizures with benzodiazepenes, such experimental drugs as progabide and vigabatrin, and other GABA-agonists further supports the hypothesized link between weakened inhibition and seizures (Bartholini, Boss, Lloyd, & Morselli, 1985).

Perception

Perception researchers have long recognized the importance of lateral inhibition and other mechanisms for suppression of neuronal activity (Nabet & Pinter, 1991). Perceptual phenomena that can be explained in terms of inhibition include classic work on Mach bands (Ratliff, 1965) and touch (von Bekesy, 1967), as well as such diverse phenomena as critical flicker fusion, binocular rivalry, masking, aftereffects and other opponent-process phenomena, figure-ground discrimination, and stimulus persistence (e.g., Barlow, 1990; Rose & Dobson, 1985). The role of inhibition in perception is illustrated here by research on receptive fields and prepulse inhibition.

Receptive fields. Lateral and other types of inhibition are used in models for on-off, direction-specific, and other types of receptive fields (Gottlieb, 1988). Of particular relevance to the contribution of inhibition, Hicks and his colleagues (Hicks, Landry, Metherate, & Dykes, 1985) have demonstrated that application of the GABA antagonist bicuculline to somatosensory cortex in cats enlarges their touch receptive fields over the following 20 to 30 min. Receptive fields gradually shrink back to their normal size as inhibitory functioning returns. Bicucilline also disrupts cortical receptive fields tuned for orientation and direction (Sillito, 1985), indicating that, in addition to excitation, inhibition is necessary for these perceptual sensitivities.

Prepulse inhibition. Prepulse inhibition is a phenomenon in which one stimulus (the prepulse) attenuates the startle response of the organism to an immediately following stimulus. In humans, for example, presenting a weak 80 db noise 250 msec prior to a loud 120 db noise reduces the eyeblink response to 50% or less of the normal response to the loud noise alone (Geyer, Swerdlow, Mansbach, & Braff, 1990). Geyer et al. (1990) review evidence on the biochemical processes involved in this suppression effect, including evidence for the contribution of GABAergic (i.e., inhibitory) neurons.

Attention

Selective attention is the capacity to process target stimuli and ignore other, potentially interfering, stimulus events (e.g., name the ink colour and ignore the colour word in the classic Stroop task). Inhibition could facilitate attention by actively suppressing distracting stimuli, much like lateral inhibition to use the analogy of Walley and Weiden (1973). The prepulse inhibition paradigm is operationally similar to selective attention paradigms and, as was found for prepulse inhibition, empirical and theoretical considerations support a contribution of inhibitory mechanisms to selective attention.

Physiological research. Physiological research provides evidence for inhibitory mechanisms in attention. For example, Moran and Desimone (1985) demonstrated that responses of single-cells in visual cortex to unattended stimuli were dramatically reduced, suggesting a filtering or gating mechanism consistent with inhibition models. Inhibition models are further supported by recent work which suggests that much processing throughout the visual system involves rivalry between competing stimuli (Desimone & Duncan, 1995).

Negative priming. One behavioral finding consistent with an inhibitory model of attention is the negative priming effect (Tipper, 1985; Houghton & Tipper, 1994, this issue). In negative priming, target items in selective attention tasks are more difficult to process when they appear as distractors on the preceding trial than when they do not appear as prior distractors. In the Stroop task, for example, it is more difficult to name the ink color ''blue'' when the prior to-be-ignored word was ''blue'' instead of a different color. According to inhibition theories, residual inhibition of the distractor must be overcome before the now-relevant response can be produced. Inhibitory processes are also implicated in attentional research on ''inhibition of return'' and related paradigms.

Figure-ground. Discrimination of figure from ground is closely related to selective attention inasmuch as the figure is generally the attended-to-element in the stimulus array. At least one associative model uses mutual inhibition to isolate figures from grounds (Kienker, Sejnowski, Hinton, & Schumacher, 1986). Reversible or ambiguous figures in which a single display provokes alternating interpretations (i.e., alternating figure-ground percepts) likewise suggest competition and mutual inhibition.

Action

A number of inhibitory processes have been identified in the motor system, with respect to both opponent processing of antagonistic peripheral motor neurons and processing in the central nervous system. Inhibitory mechanisms have also been proposed for several behavioral phenomena in research on movement.

Physiological evidence. The cerebellum plays an important role in movement and does so exclusively by way of inhibitory output from Purkinje cells (Brooks, 1986; Eccles, 1977; Nicholls et al., 1992). Eccles (1977) compared the cerebellum to a sculptor because both operate by carving away unwanted elements, in the case of the cerebellum by inhibiting irrelevant components of movement.

Proximity effects. The similarity of competing actions affects the speed with which one response can be selected. Kornblum (1965), for example, showed that pressing a key with the right middle finger was faster if the competing response was the index finger of the other hand rather than the same hand. Kornblum hypothesized that a recently activated neighbouring finger (i.e., same hand or same hemisphere) is more difficult to inhibit than a distant finger. Alternatively, residual inhibition of subsequent responses by prior responses may be greater for near than for far fingers.

Uncertainty effects. A second motor phenomenon that can be explained by inhibitory mechanisms is the uncertainty effect, in which motor RTs slow with increases in the number of alternative responses that can occur on any trial (see review by Jensen, 1987). Although this robust phenomena can be explained by a serial search process or by dilution of activation along multiple pathways, an inhibitory explanation is that making a specified response entails suppression of competing responses. RT therefore slows with increases in the number of recently active (or potential) responses that must be suppressed and that act in turn to suppress the response required on the current trial.

Learning and Episodic Memory

The areas of learning and episodic memory include many phenomena that implicate inhibitory mechanisms, including some learning phenomena that are explained in terms of inhibitory processes already discussed. Latent inhibition, for example, has been characterized by some as an attentional phenomenon (Lubow, 1989).

Conditioning. Pavlov (1927) advocated very early on that inhibitory mechanisms play central roles in behavior. The prototypical example of inhibition in Pavlovian conditioning is a CS that is paired with a US less often than the US occurs in the absence of any CS. This conditioned inhibitor reduces responding when paired with excitatory CSs and resists being reconditioned as an excitor. Williams, Overmier, and LoLordo (1992) articulate the case for these criteria, provide a brief history of the concept of inhibition in learning, and demonstrate that inhibitory mechanisms appear to be necessary to explain the effect.

Interference effects. The classic interference and transfer paradigms used in human learning and episodic memory studies implicate inhibitory processes. In the retroactive interference paradigm, for example, intervening

lists suppress retrieval of first-list responses when shared stimuli are used across successive paired-associate lists. Interference is stronger for similar responses than for unrelated responses. Winocur, Moscovitch, and Bruni (this issue) use this paradigm to examine interference effects as a function of head injury and aging. A number of other retrieval blocking effects also occur in episodic memory tasks (Roediger & Neely, 1982). For example, providing half of the items in a list as retrieval cues can reduce recall for the remaining items. One hypothesis is that the presented cues interfere with to-be-recalled items via lateral inhibition; that is, activation of mental representations for presented items suppresses representations for nonpresented items, making the latter more difficult to retrieve.

Semantic Memory

Inhibitory mechanisms have also been shown to play important roles in retrieval from semantic memory. Semantic memory stores the meanings of words, labels for objects, and other knowledge that organisms have about their worlds. One conceptualization of retrieval from semantic memory is that a stimulus activates a collection of internal representations from which the eventual response is selected. This characterization suggests that semantic retrieval involves processes highly similar to those that underlie selective attention, perhaps including suppression of internally-generated competing responses analogous to the externally-presented distractors in selective attention. Given this isomorphy, it would not be surprising if similar brain mechanisms performed ''response'' selection in attention and semantic retrieval.

Semantic retrieval tasks. Semantic retrieval tasks include such tasks as free association, production of instances from superordinate categories and other fluency tasks, confrontational picture naming, and mental arithmetic. Uncertainty effects, perhaps due to mutual inhibition among alternatives, have been observed in various semantic retrieval tasks (Clark, 1991; Johnson, 1994); for example, subjects are slower to name pictures with multiple alternative labels than pictures with one or a few labels (Lachman, 1973; Paivio, Clark, Digdon, & Bons, 1989). In retrieval of mental arithmetic facts, subjects temporarily suppress recently retrieved number facts that would otherwise interfere with later problems (Campbell & Clark, 1989). Additional evidence on the nature of inhibitory mechanisms in number fact retrieval is described by Clark (1992) and by Campbell and Arbuthnott (this issue). Other inhibition phenomena in semantic memory include the tip-of-the-tongue phenomenon and various types of retrieval blocking (Brown, 1991; Roediger & Neely, 1982) and suppression of the irrelevant meaning of homonyms in selective attention (Marcel, 1980) and sentence comprehension (Gernsbacher & Faust, 1991) paradigms.

Word identification. Inhibitory mechanisms also operate at a word identification level prior to semantic retrieval. In the case of auditory word identi-

fication, primes disrupt recognition of phonetically similar targets (Goldinger, Luce, Pisoni, & Marcario, 1992). This finding suggests that sounds activate a collection of phonetically similar representations and either that mutual inhibition of incorrect competitors is more difficult when competitors are primed or that the primes directly suppress and thereby slow down access to the phonetic codes of subsequent targets. Such inhibitory links between competing representations are also incorporated in connectionist models for visual word identification (e.g., McClelland, 1991).

Emotion, Personality, and Psychopathology

In addition to basic neuronal and cognitive processes, inhibition has been implicated in many psychological states and conditions that concern emotion, including anxiety, depression, ADHD, impulsivity, conduct disorder, and obsessive-compulsive disorder (Rapoport, 1989). One indicator of the widespread involvement of inhibitory processes in psychopathology is the proposal that weakened inhibition may provide a general model for psychopathology (Gorenstein & Newman, 1980). This broad domain is represented here by research on schizophrenia and aggression.

Schizophrenia. Considerable experimental evidence indicates that schizophrenia is associated with weak inhibitory functioning. Geyer et al. (1990) have found that prepulse inhibition is lower in schizophrenics than in controls. Beech and Claridge (1987) demonstrated that people who scored high on a schizotypy scale did not show the negative priming effect (i.e., suppression of distractors) typically found in selective attention for normal and low schizotypy subjects. Attentional dysfunctions, perhaps resulting from diminished inhibition, have been the basis for several models of schizophrenia (Gjerde, 1983; Lubow, 1989). The hypothesis of weakened inhibition is also consistent with early models that related cognitive dysfunctions of schizophrenia to ''loosened'' associations (Meehl, 1990), that is, failure to selectively inhibit spreading activation in a semantic network would lead to remote and unusual verbal associations.

Aggression. Several lines of evidence support a link between weak inhibition and aggression. Most directly, Mandel, Ciesielski, Maitre, Simler, Mack, and Kempf (1979) demonstrated that experimental disruption of GABA functioning increases aggressive behavior in rats. Some researchers have also reported that aggression is a common occurrence in temporal lobe seizure and that a somewhat elevated percentage of people arrested for violent crimes have abnormal EEG recordings (Mark & Ervin, 1970; Rosenzweig & Leiman, 1989, p. 599). The effect of frustration (i.e., elevated arousal) on aggression (e.g., Berkowitz, 1983) suggests a suppressing role for inhibitory mechanisms in the control of aggressive behavior, and weak inhibitory controls over aggressive impulses have been implicated in the behavior of psychopaths (Hare, 1993).

Except for psychopathology, the present overview has focused on relatively basic behaviors. However, the processes that underlie such basic cognitive functions as attention and learning can also explain such high-level cognitive functions as complex language, thinking and problem solving, and intelligence. To illustrate, comprehension of metaphors (e.g., ''Inhibition is a tyrant'') may require suppression of semantic features irrelevant to the metaphoric meaning (e.g., that tyrants are people).

The framework can also accommodate some contemporary social findings and theories, many of which are already described in terms of schemas and related cognitive constructs. For example, emotional expressiveness to sexual stimuli is greater in the presence of friends than alone (Buck, Losow, Murphy, & Constanzo, 1992), an effect that can be modeled by disinhibition (i.e., the presence of friends inhibits associative connections that normally inhibit facial expressions associated with arousal).

This brief review and the other papers in this special issue demonstrate much direct and indirect support for the idea that inhibitory mechanisms contribute to behavior in diverse areas of psychology. If this view of the output side of Fig. 1 is correct, a second question is whether the evidence also supports the model's assumption that inhibitory mechanisms are affected by the various causal factors represented in Fig. 1.

INHIBITORY MECHANISMS AND CAUSAL FACTORS

Evidence for the hypothesized relationships between the causal factors in Fig. 1 and the mediating construct of inhibition comes from diverse sources and varies in quality. Some evidence is based on relationships between the causal factors and relatively direct indicators of inhibitory functioning (e.g., seizures, negative priming), whereas other evidence involves relationships with variables for which the role of inhibition is more inferential (e.g., uncertainty effects, susceptibility to interference). The collective weight of these different grades of evidence is persuasive in several domains and less so in others.

Table 2 lists representative findings and theory that are consistent with the expected relationships between the causal factors and the underlying construct of inhibition. The capacity of the inhibition model to provide a unified explanation for diverse phenomena is particularly evident in research on childhood development and aging.

Childhood Development and Aging

The literature on childhood development and aging shows many physiological and behavioral phenomena suggesting that the relative strength of inhibition increases during childhood and decreases with advanced age. If inhibition contributes to diverse behaviors, as suggested by the present model, one should therefore observe numerous curvilinear relationships be-

TABLE 2
Causal Factors and Inhibition

Hypoxia
Physiology: *In vitro* studies (Dunwiddie), head injury and seizures (Ransohoff)
Behavior: Amplified reflexes (van Harreveld), irritability and confusion (Caplan), uncertainty and naming (Mills), interference and digit naming (Campbell & Clark)
Trauma and disease: Head injury, accidents, disease (stroke, asthma, anemia, . . .)
Aging
Physiological: VEPs (Dustman), seizures (Engel; Hauser & Hesdorffer)
Behavioral: Cognitive (Kausler), negative priming (Tipper), unrelated prime interference (Bowles)
Theories: Inhibition (Dustman; Hasher & Zacks), susceptibility to interference (Winocur), inverse ontogeny (Reisberg)
Brain localization
Frontal lobes: Perseveration on WCST, interference (Shimamura), aggression and impulsivity
Lateralization: Figure-ground (Cronin-Golomb), finger movements (Kimura), priming (Chiarello)
Theories: Frontal lobes and inhibition (Luria; Diamond) or executive functions, hemispheres and analytic vs. holistic or sequential vs. simultaneous processing
Childhood development
Physiological: Seizures (Engel; Hauser & Hesdorffer), VEPs (Dustman)
Behavioral: Stroop (Comalli), negative priming (Tipper), impulsivity (Diamond), uncertainty, grasping, conservation tasks (Piaget)
Theories: Inhibition (Bjorklund & Harnishfeger; Dempster; Dustman), frontal lobes (Diamond), reversibility (Piaget), primary thinking (Freud)

tween inhibition-related behaviors and developmental age across the lifespan.

Physiological indicators. Epidemiological studies of seizure susceptibility show a marked decline from birth to early adolescence (Hauser & Hesdorffer, 1990), suggesting weakened inhibition (or exaggerated excitation) during early childhood. Susceptibility to seizures also increases in the elderly, at least according to epidemiological studies done in North America (Engel, 1989; Hauser & Hesdorffer, 1990). The increase in seizures during aging is consistent with the negative correlation between age and post-mortem measures of GABA levels (Glick, Ross, & Hough, 1982).

The predicted curvilinear relationship has also been found between age and the correlation between visual evoked potentials to patterned and unpatterned stimuli (Dustman et al., 1990, this issue). That is, evoked potentials to patterned and unpatterned stimuli become less similar during childhood, suggesting stronger lateral inhibition, and more similar in the elderly, suggesting weakened lateral inhibition.

Behavioral evidence. Many behavioral phenomena that implicate inhibition show improvements in performance during childhood and declines during old age. The Kausler (1991) volume on experimental psychology, cog-

nition, and aging, for example, documents numerous changes in such inhibition-related behaviors as increased stimulus persistence, and increased interference in memory tasks.

With respect to attention, Comalli, Wapner, and Werner (1962) showed that interference on the Stroop task decreases during childhood and increases during old age. Subsequent research on negative priming effects has produced specific evidence for absent or weak suppression of distractors in young children and older adults (Tipper, Bourque, Anderson, & Brehaut, 1989; Tipper, 1991).

Changes in motor skills provide additional evidence for weak inhibitory functioning during childhood; for example, choreiform movements indicate failure to suppress the contralateral hemisphere, exaggerated uncertainty effects suggest difficulty suppressing competing alternatives (Hemmelgarn & Kehle, 1984), and the gradual development of a finely tuned index–thumb grasp entails inhibition of movement in the three unused fingers. Some of these developmental effects, such as exaggerated uncertainty effects in choice RT, have also been reported for the elderly (Kausler, 1991).

With respect to retrieval of information from semantic memory, there is evidence that both young children and elderly adults have difficulty suppressing competing responses that interfere with retrieval of the target response. Clark and Johnson (1994), for example, found that young children asked to generate superordinate names for pictured objects (e.g., ''toy,'' ''clothes'') have particular difficulty suppressing the more readily available instance names (e.g., ''ball,'' ''shirt''). Access to superordinate information may be similarly disrupted in the elderly (Hartley, 1988). Age-related difficulties in inhibiting irrelevant associates in semantic memory are also suggested by Bowles, Obler, and Poon's (1989) finding that interference from distracting primes in a definition task was larger for older adults than for younger adults.

Tasks sensitive to impulsivity also provide evidence for strengthened inhibition during childhood development, including a decrease in errors on the game ''Simon Says'' (Strommen, 1973; Diamond, 1991), lower scores on the Conners rating scale norms for Attention Deficit Hyperactivity Disorder (Goyette, Conners, & Ulrich, 1978), and both fewer errors and slower RTs on the Matching Familiar Figures test. Although the elderly tend to be seen as cautious, rather than impulsive, they also demonstrate behavioral and cognitive changes that may be related to some of the impulsivity tasks studied with children. For example, the failure of children to suppress normal actions in ''Simon Says'' parallels a decreased capacity to inhibit dominant cognitive responses (i.e., decreased cognitive flexibility) in the elderly (Kausler, 1991).

The literature on emotional changes across the life-span is also suggestive of a curvilinear relationship between age and inhibition, but the evidence is quite incomplete and difficult to ascribe with much confidence to inhibitory processes alone. According to some reports, the elderly do show increased

levels of anxiety and other negative emotions that have been associated with weakened inhibition (Hersen & Van Hasselt, 1992). It is unclear, however, whether the expected decrease in anxiety and fear occurs during childhood, inasmuch as declines in some fears (e.g., personal safety, imaginary creatures) are offset by increases in other domains (e.g., school, social relationships) and there are non-inhibitory explanations for the changes (Hetherington & Parke, 1986, pp. 269–270).

Theories of child development and aging. The present hypothesis of age-related changes in inhibitory functioning has previously been advanced by several scholars, including Bjorklund and Harnishfeger (1990), Dempster (1992), and Dustman et al. (1990). The inhibition framework also overlaps with neuropsychological models that ascribe a central role in development to the frontal lobes (Diamond, 1991), which have long been associated with such inhibition-related competencies as self-regulation and impulse-control. With respect to theories of aging, age-related changes in performance have also been attributed to inhibition by Dustman et al. (1990), Hasher and Zacks (1988), and other researchers.

One strength of the inhibition framework is that it permits existing theories of development to be translated into more mechanistic terms. Inhibition is suggested directly by such Piagetian constructs as reversibility, decentration, and egocentrism, all of which implicate suppression of a person's current view in order to imagine an alternative feature or perspective. Freud's depiction of primary process thinking similarly suggests that childhood is characterized by uninhibited primal impulses.

Several hypotheses about the neuropsychological effects of aging are similarly amenable to an explanation in terms of inhibitory dysfunction. Distractibility or susceptibility to interference (Winocur, 1982; Winocur et al., this issue), for example, has been proposed to account for age-related declines in cognitive functioning. This model suggests a diminished capacity to suppress distracting or interfering events. Reisberg, Pattschul-Furlan, Franssen, Sclan, Kluger, Dingcong, and Ferris (1992) proposed the hypothesis that dementia during aging recapitulates ontogeny inversely. This hypothesis of reverse homology emerges from the present model because decreased inhibition during aging mirrors increased inhibition during childhood development.

The inhibition model thus provides a plausible account for various developmental changes across the life-span and for several current explanations for those changes. Moreover, the assumption of weakened inhibition during aging can itself be derived from a more basic relationship between hypoxia and inhibitory functioning, the next topic to be examined.

Hypoxia and Inhibition

A second area that demonstrates the potential for unified explanations of diverse phenomena centers on the possible effects of hypoxia on inhibitory

functioning and inhibition-related behaviors. Hypoxia, as opposed to other mechanisms of brain insult, is emphasized here for several reasons, notably because it is implicated in a broad array of conditions, the brain is particularly sensitive with respect to its oxygen requirements (Sudarsky, 1990), and hypoxia may have particularly damaging effects on inhibitory functioning.

Hypoxia can result from diverse events or physiological conditions that compromise delivery of oxygen to the brain, including myriad diseases (e.g., pulmonary conditions, cardiovascular disease, anemia), various kinds of brain trauma (e.g., ischemia, head injury), and unusual environmental circumstances (e.g., altitude, drowning, carbon monoxide). Various non-neurological conditions that disrupt oxygen delivery have neuropsychological consequences, such as Chronic Obstructive Pulmonary Disorder (Krop, Block, & Cohen, 1973), sleep apnea (Berry, Webb, Block, Bauer, & Switzer, 1986), and diabetes (Kovacs, Goldston, & Iyengar, 1992). Both short-term and long-term cognitive dysfunctions can result from exposure to even moderate altitudes (Bahrke & Shukitt-Hale, 1993; Kramer, Coyne, & Strayer, 1993).

One tentative assumption is that the psychological and neurological consequences of these conditions are mediated in large part by hypoxia and that these literatures could be relevant to the direct brain insults that have been more commonly studied. The assumption is tentative because head injury, ischemia, and other brain insults are associated with diverse structural and biochemical changes, making it difficult to isolate the pure effects of hypoxia. Nonetheless, the available neuroscience and behavioral evidence is sufficiently consistent to warrant continued investigation of the potentially unifying hypothesis that decreased inhibition is part of a common pattern of reactions to diverse conditions that compromise oxygenation of the brain, including direct brain insults. Research has shown, for example, that manipulation of hypoxic effects separate from other physiological concomitants of naturally-occurring ischemia can reproduce some of the neurological effects associated with standard experimental ischemia (Salford, Plum, & Siesjo, 1973).

Of special interest here is suggestive evidence that inhibitory mechanisms may be particularly vulnerable to hypoxia. This evidence comes from diverse sources, including basic neurophysiology and behavioral research.

Physiological findings. That inhibitory neurons are more vulnerable to hypoxia than are excitatory neurons has been directly demonstrated in some single-cell *in vitro* studies (e.g., Dunwiddie, 1981), although not all studies have obtained this effect.

Converging evidence for a weakening of inhibition comes from physiological phenomena related to seizures, one indicator of possible inhibitory dysfunction. In the laboratory, tremors, convulsive movements, spasticity, and other signs of seizure are characteristic of experimental hypoxia (Hansen, 1988; Windle, 1952). With respect to naturally-occurring brain insults, sei-

zures occur 50% or more of the time in cases of cerebral laceration or penetrating head wounds and as much as 5% of the time in minor closed head injury (Ransohoff, 1982). Such figures may even be conservative as anti-seizure medication is commonly administered prophylactically in cases of head injury and hypoxic insult. Such anti-seizure medications often work by enhancing inhibition or interfering with excitation (Engel, 1989, Chapter 15).

Behavioral evidence. Hypoxia is associated with diverse behavioral changes that suggest inhibitory dysfunction. Early physiological researchers such as van Harreveld (1939) demonstrated that reflexes were exaggerated at reduced oxygen levels, suggesting that hypoxia weakened a counteracting inhibitory mechanism. Carbon monoxide poisoning produces such inhibition-related symptoms as irritation, giddiness, confusion, and disturbance of judgement and in chronic cases can be mistaken for epilepsy (Caplan, 1982). The symptoms of hypoxia mimic those of acute alcohol intoxication and overlap with symptoms of frontal lobe damage, two areas that have been characterized in terms of weakened inhibition, as discussed below.

Hypoxia may also contribute to the many cognitive difficulties associated with brain dysfunction that suggest selective damage to some inhibitory capacity to suppress competing responses. Such findings include susceptibility to interference from similar alternative responses in digit naming (Campbell & Clark, 1988), and elevated picture naming RTs and errors primarily for high uncertainty pictures with many alternative names (Mills, Knox, Juola, & Salmon, 1979).

Hypoxia, disease, and aging. The link between hypoxia and inhibition is an important one in unifying neuropsychological research and theory, because so many diseases and conditions can compromise delivery of oxygen to the brain. As noted above neuropsychological dysfunctions are of course associated with strokes, but are also associated with disorders that indirectly affect brain functioning, such as heart attacks, open heart surgery, asthma, chronic obstructive pulmonary disorder, and anemia. Compromised oxygenation of the brain and selective damage to inhibitory neurons could contribute to the behavioral effects of these and other medical conditions.

The links between hypoxia, disease, and inhibition may also provide an ultimate explanation for the relationship between aging and inhibitory dysfunction. Aging could be associated with weakened inhibition because of age-related changes in respiration, circulation, cardiac functioning, hemoglobin, and other physical systems that compromise oxygen delivery to the brain (Elias, Elias, & Elias, 1990). These same physiological changes are implicated in the beneficial cognitive effects of exercise in the elderly (Dustman et al., 1990) and of drugs that enhance circulation, although the latter findings are controversial.

The inhibition framework thus provides a unified, albeit speculative, explanation for diverse phenomena associated with brain insult and related conditions. The proposed hypothesis that some effects result from inhibitory

dysfunctions still permits additional consequences specific to different types of brain insult and different areas of damage, although research on localization of function has also implicated inhibitory processes.

Brain Localization

The specialization of different regions of the brain for particular functions has produced both findings and theoretical mechanisms suggesting that regions might be differentiated in part with respect to inhibitory function. This hypothesis is particularly relevant to research on frontal lobe functioning and on cerebral lateralization.

Frontal lobe function. The frontal lobes are commonly associated with inhibition and related constructs. Phenomena suggestive of inhibitory dysfunction in frontal lobe patients include attentional difficulties, perseverative errors on the Wisconsin Card Sort, susceptibility to interference in memory tasks (Shimamura, Janowsky, & Squire, 1991), and such behavioral disturbances as irritability, aggression, impulsivity, and disregard for consequences of actions (see chapters in Levin, Eisenberg, & Benton, 1991). The frontal lobes have also been implicated in various conditions for which there is converging evidence of inhibitory dysfunction, such as schizophrenia (Mirsky & Duncan, 1986) and perhaps psychopathy (Hare, 1993).

The possible role of inhibition has long been recognized in theorizing about the frontal lobes (e.g., Luria, 1966; Levin et al., 1991). Planning, executive control, and related processes commonly associated with the frontal lobes are readily translated into inhibitory mechanisms. To plan or control, for example, means that one must activate possible courses of action but temporarily or permanently suppress their actual execution.

Lateralization phenomena. Inhibition has also been implicated in the functioning of the cerebral hemispheres, both with respect to differences between the hemispheres and their interaction with one another. Some behavioral evidence suggests greater inhibition within the left hemisphere, although post-mortem levels of GABA do not confirm this hypothesis (Glick et al., 1982). Cronin-Golomb (1986) found with split-brain patients that only the left hemisphere recognized figures better than grounds, suggesting stronger inhibition of the background in the left hemisphere. Kimura (1976) found that the right hand was better than the left at sequential finger movements, whereas the left hand was better at forming simultaneous patterns. If sequential movements involve suppression of other fingers and simultaneous movements involve non-suppression, these findings too suggest stronger inhibition for the left hemisphere. Chiarello (1988) reviewed cognitive findings consistent with more robust inhibition in the left hemisphere, such as more focused spreading activation and greater suppression of irrelevant meanings of homonyms.

With respect to relationships between hemispheres, Chiarello and Max-

field (this issue) review research on interhemispheric inhibition and document some complexities that face simple inhibition models.

Many characteristics ascribed theoretically to the two hemispheres can be explained by inhibitory models. Such distinctions as analytic vs. holistic, or sequential vs. simultaneous suggest such inhibitory mechanisms as attention to specifics and suppression of distracting details versus keeping all components equally activated without any being overly dominant (i.e., without inhibiting other elements in the percept or cognition). Inhibitory mechanisms thus provide one way to implement processes described at a more abstract level, as was also shown earlier with examples from childhood development and aging.

Other Causal Variables

The present summary by no means exhausts the causal variables that benefit from an inhibitory analysis. Other causal factors that have been or could be explained in terms of inhibition include the acute effects of alcohol (Steele, 1986), effects of ECT on depression and other psychiatric conditions (Coffey, 1993), and a host of therapeutic drug effects (e.g., benzodiazepenes and anxiety reduction).

Parenting and other socialization factors can also be accommodated within the inhibition framework. For example, parents vary in the extent to which they model and explicitly teach self-control, and disinhibition models have been proposed to account for the effects of media on aggression (Josephson, 1987).

Evidence for the heritability of psychiatric disorders, intelligence, and other behaviors related to those cited here raises the possibility that some genetic effects might reflect underlying inhibitory mechanisms. The proposed ties between behavioral and neuronal inhibition, for example, provide a possible link between research on behavioral heritability and fundamental biological research on the genetics of GABA and other underlying biochemical processes (Farrant & Cull-Candy, 1993).

DISCUSSION

The preceding review illustrates the potential for unified explanations of diverse causal effects in terms of inhibitory mechanisms. Although considerable speculation underlies the present conceptualization, evidence does exist for many hypotheses incorporated in Fig. 1 and some of the hypotheses have withstood critical evaluation (see other papers in this special issue). The remainder of the paper addresses some potential concerns about the proposed approach.

Universal versus Specific Effects

Figure 1 might initially suggest a monolithic inhibitory process that will operate uniformly across all tasks and will be uniformly disrupted by relevant

causal factors. This characterization of the model is incorrect, or at least premature. The hypothesis of a central role for inhibition in diverse areas, for example, is still perfectly consistent with selective damage to regions of the brain specialized for particular functions.

On the other hand, it is also possible that certain areas of the brain do indeed exert inhibitory control over diverse functions, resulting in global dysfunctions. If frontal lobe inhibition contributes to many facets of cognitive and emotional control, for example, weakened inhibition could be reflected in such diverse areas as attention, semantic retrieval, episodic memory, impulsivity, and aggression. The notion of general inhibition is consistent with relatively high levels of co-morbidity for various disorders in which inhibition has been implicated (e.g., anxiety and depression) and perhaps with the finding that post-mortem levels of one indicator of GABA were correlated across different brain regions (Glick et al., 1982). That is, individuals with high levels of GABA in one region of the brain tended to have high levels in other regions, suggesting that individual differences in inhibitory functioning may be relatively uniform across different functional areas of the brain.

Need for Further Development

The proposed framework clearly requires much additional empirical and theoretical work. The inhibitory component is quite inferential in many of the studies cited here, leaving doubts about the contribution of inhibition. Such doubts are best addressed by searching for as direct evidence as possible that inhibitory mechanisms indeed underlie the observed relations, using negative priming, VEPs, and related paradigms sensitive to inhibitory functioning.

Considerable theoretical work is also needed to develop mechanistic models. Without detailed mechanistic models, it is difficult to determine the compatibility of inhibition and competing views, or to design strong tests of their relative merits. At present, many psychological models are not stated in sufficiently concrete terms to even know whether inhibitory mechanisms underlie the hypothesized processes. One cannot, for example, test definitively whether inhibition or sequential processing views better characterize hemisphere differences without a mechanistic model for sequential processing that does not involve inhibition.

Benefits of Unified Theory

The general goal of this paper is to identify universal mechanisms that permit construction of mechanistic models for phenomena in diverse domains. In psychology and neuropsychology, researchers tend to emphasize analysis of particular paradigms and phenomena more than synthesis across different domains. When synthesis is attempted, it can be so abstract that

concrete models for specific phenomena are only connected loosely, at best, to the general theory. The present approach strives for both generality and specificity; inhibition is a pervasive construct, yet one that permits the ready development of specific inhibitory models for diverse phenomena.

In conclusion, the present framework examines superficially distinct areas, with a view to understanding how such fundamental constructs as inhibition can provide mechanistic explanations for phenomena in diverse areas of psychology, neuropsychology, and related neuroscience disciplines.

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