

Attention and Attentional Dysfunction

Anne B. Sereno

Higher cognitive functions, such as attention, memory, or language, are usually taken for granted. Only when a disruption in these functions occurs do we realize how critical they are to everyday life. Attentional dysfunction is a hallmark of many human disorders, including mental disorders (e.g., schizophrenia), neurological disorders (e.g., strokes or Parkinson's disease), and developmental disorders (e.g., attention deficit hyperactivity disorder). However, attention can mean many different things. It may involve searching for something, holding information in memory, or ignoring irrelevant information.

BEHAVIORAL STUDIES

If we are to make progress in treating attentional dysfunction, it is important to be able to define attention clearly. One way to distinguish between different notions of attention is to relate these concepts to their underlying neurophysiological mechanisms.

Overt and Covert Orienting. Saccadic eye movements (EMs) are *overt* shifts of the eyes that marshal processing resources by focusing the fovea on the object of interest. The fovea, compared to the rest of the retina, is grossly over-represented in the visual parts of the human brain. Spatial attention is the *covert* shift of processing resources that accompanies or even precedes overt shifts of the eyes. Such covert shifts can occur without an accompanying EM—we do not always look at the location that has captured our interest. This dissociation has led many researchers to ignore the relationship between spatial attention and EMs. However, in our laboratory, we hypothesize that spatial selective attention (i.e., attention that is directed to a particular spatial

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Impulsivity and its Disorders

Alan C. Swann

One of the brain's basic functions is the control of goal-directed, drive-related behavior, whether 'spontaneous' or in response to some external stimulus. Successful regulation of the initiation of behavior requires a balance between speed and the ability to conform behavior to its external and internal context. Part of this balance is the behavioral entity that is often called 'impulsivity.'

Impulsivity is like art. It appears easy to grasp intuitively, but a rigorous definition is elusive. Also like art, any behavior can be impulsive or non-impulsive. For our purposes, we will define impulsivity as inability to conform behavior to its internal or external context. We will discuss the mechanisms by which speed is balanced by response to context, the manner in which failures of this mechanism might lead to behavior that is called 'impulsive', measurement of impulsivity, its role in psychopathology, and its treatment.

PHYSIOLOGY AND MEASUREMENT OF IMPULSIVITY

The initiation of behavior involves Morgenson's circuit or the motive circuit, which consists largely of a dopaminergic system including the ventral tegmental area, the caudate nucleus, and the nucleus accumbens. During the first few tenths of a second after the initiation of potential behavior, feedback mechanisms based on the environment and on relevant memory, which involve the prefrontal cortex, amygdala, and hippocampus, can apparently prevent or modify motivated behavior. Damasio's group has shown that the brain recognizes potentially appropriate or inappropriate responses before the response reaches conscious awareness. Certain individuals with pathological impulsivity, including lesions of the prefrontal cortex, lack this apparent

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location) shares a close physiological relationship with saccadic EMs. If EMs are physiologically related to spatial attention, our understanding of their neural organization is crucial in clarifying attentional mechanisms.

Physiological Model Relating Overt and Covert Orienting. Based on work from many different labs using a variety of techniques, we have proposed a model of orienting defined by two separate orienting systems. A voluntary orienting system controls voluntary attention and voluntary EMs (e.g., looking for your car in a parking lot). Under normal circumstances, this system continually inhibits a second, reflexive orienting system that controls reflexive attention and reflexive EMs (e.g., looking towards a sudden flash of light). Areas of prefrontal cortex play a critical role in voluntary orienting, whereas the superior colliculus, a subcortical area, plays a critical role in reflexive orienting. This dual process model has provided a framework, as illustrated below, for understanding attentional dysfunctions, predicting performance, and even forecasting drug effects.

Schizophrenia. Various studies have shown decreased frontal activity in schizophrenic patients. One prediction of our interactive dual process model is that a deficit in the voluntary system will produce poor performance on voluntary tasks but also hyper-performance on reflexive tasks. We observed just such a pattern of orienting in schizophrenic patients.

In a review of the literature on stimulant and depressant drug use in schizophrenic patients, a conspicuous pattern emerges: patients show increased use of stimulants and decreased use of depressants. We have found a similar pattern in legal drug habits (nicotine and caffeine vs. alcohol) of normal subjects that score high on a standardized test of schizotypy. An unusually high percentage of schizophrenic patients smoke (approximately 80-90% vs 30% in the normal population). Imaging studies have shown that nicotine administration increases cortical activity in the frontal lobes. According to our model, when nicotine acts to increase cortical or voluntary activity, it likewise increases cortical inhibition of the subcortical reflexive system. Thus, in schizophrenic patients, increased cortical activity should improve functioning of the deficient voluntary system and inhibit the overactive reflexive system. Hence, as others have proposed, smoking may be a form of self-medication in schizophrenic patients. In our lab, tests of normal subjects show that nicotine administration, in the form of chewing gum, improved performance on a voluntary EM task but reduced performance or had no effect on reflexive tasks. We have also shown that for schizophrenic patients who show deficits on a voluntary EM task, nicotine administration improves their performance on this task.

Parkinson's Disease. As in schizophrenia, a dysfunction of prefrontal cortex has also been implicated in Parkinson's disease (PD). We have recently demonstrated that PD patients show severe deficits in voluntary orienting tasks but equal or better performance than normals in reflexive orienting tasks. We are now investigating whether customary medications normalize these cognitive and EM dysfunctions.

Spatial Selective Attention. Recent neurophysiological and neuropsychological data contradict the intuitive and popular notion that spatial selective attention is a single entity. In fact, *several* cortical areas represent space. These various cortical areas are also involved in motor programming for different effectors (e.g., EMs vs. hand movements). In a series of experiments in normal subjects, we have shown that there is a unique time course of attentional effects (both facilitatory and inhibitory) dependent upon the response of the subject. Typically, after presentation of a peripheral cue, at short intervals subjects respond faster to a target if it happens to occur in the cued location. At longer intervals, subjects respond slower to targets at this location (inhibition of return). We found that there is a range of cue-target intervals during which saccadic responses are inhibited by spatial cues, whereas manual responses to the same cued positions are facilitated. That is, for the same task, making a left or right EM vs. pressing a left or right key results in different attentional effects.

SINGLE UNIT STUDIES

Prefrontal cortex has undergone great expansion in primate evolution and accounts for nearly 30% of the total cerebral cortex in humans. The greater relative magnitude of human prefrontal cortex has long been presumed to indicate that this cortex is the substrate for neural activity responsible for regulating the most complex behavior, such as attention and short-term memory. The question of whether there is functional specialization in prefrontal cortex has become a central focus of work in cognitive neuroscience. Strikingly different views of the functional architecture of prefrontal cortex have been put forward in recent years. Although some investigators have proposed that prefrontal cortex is the site of integration of neuronal signals that are distinct in posterior parietal and inferior temporal cortices, others have argued that it retains a high degree of regional specificity. One of our goals is to clarify the functional organization of prefrontal cortex and its relationship to areas in posterior parietal and inferior temporal cortices.

Temporal vs. Parietal Pathways. The visual system is an excellent framework in which to examine neural mechanisms of attention because it is the most extensively studied and best characterized sensory system. Much

research has suggested that *visual processing* proceeds along two anatomically segregated streams in cerebral cortex: a ventral and a dorsal pathway. Each pathway comprises a different series of cortical visual areas and supports distinct functions. The ventral stream includes areas of temporal cortex and is involved in shape and object recognition (the 'what' pathway), whereas the dorsal stream includes areas of parietal cortex and is important for vision related to space (the 'where' pathway). This distinction between object and spatial properties is important in understanding the mechanisms of *attentional* effects. Modulation of cell response arising from attention to object properties (e.g., color or orientation) has been reported in the later stages of the ventral pathway (e.g., inferotemporal cortex, IT), whereas modulation of cell response due to attention to spatial location has been reported in the later stages of the dorsal pathway (e.g., the lateral intraparietal area, LIP). An important question in understanding brain mechanisms of attention is whether attention to object properties and attention to spatial location remain anatomically segregated in prefrontal cortex. The parietal and temporal pathways in visual cortex interact and both project to prefrontal regions. Careful manipulation of attention to object properties apart from attention to spatial location has rarely been performed in either physiological or psychological experiments.

Attention and Memory for Shape vs. Space. We have explored the degree of segregation of different attentional effects in cortical neurons by recording from single neurons in monkeys. We first trained the monkeys to perform one task requiring them to attend to and remember the shape of simple 2D geometric forms and a second task requiring them to attend to and remember the spatial location of these shapes. Both tasks presented identical visual stimuli and required identical EM responses, allowing us to dissociate, at the cellular level, visual stimulus and response selectivities from the effects of two different forms of attention and memory. For example, a shape (triangle) is presented in an offset position from the point of fixation. After a brief delay during which the monkey maintains its initial fixation, an array of various shapes appear encircling this fixation. In the shape memory task, the animal is required to make an EM to the remembered shape (triangle) and in the spatial memory task, to the remembered location (the initial position of the triangle).

Parietal Pathway. Unexpectedly, we found shape ('what') selective responses in area LIP, an area in the dorsal or 'where' pathway. That is, many units showed a change in activity when different shaped objects were present. Many units also showed a difference in activity during the delay period of memory tasks depending on the shape to be remembered. These findings are especially surprising since

our experiments involve shapes that the animal did not (and could not) manipulate, and thus demonstrate a type of shape selectivity equivalent to any demonstrated in the ventral pathway.

Secondly, we found little evidence in LIP (dorsal pathway) for an attentional neural signal that encoded the aspect of the sample object that was relevant on a particular trial. That is, the spatially selective delay period activity was equally prominent even when the animal was attending to the shape of the sample. Hence, our data suggest that the pervasive spatially selective delay activity found in this region of the brain is not specifically linked to voluntary attention (or memory), but instead may reflect a more reflexive process.

Temporal Pathway. In contrast, we found that the sensory response of many cells in anterior IT (AIT), an area in the ventral or 'what' pathway, depended on whether the animal was performing the shape or spatial attention task. These units showed an enhanced response to the object shape when the animal needed to attend to and remember the object's shape vs. its location.

Prefrontal Areas. Both LIP and AIT project to prefrontal cortex. Few studies have examined attention (and memory) for shape and space in prefrontal cortex, and no study has controlled for sensory and response conditions across the two kinds of tasks. This lack of control may be one reason for disparate findings. Even if memory for shape and space is not strictly segregated in prefrontal cortex, it is possible that regions of prefrontal cortex that receive input from posterior parietal areas may show a pattern of findings similar to LIP, whereas regions that receive input from inferior temporal areas may show a pattern similar to AIT. Our current research addresses such questions.

CONCLUSIONS

Approaching the cognitive process of attention from multiple levels has been productive. We believe that such an approach has resulted in two critical changes in understanding cognitive processes. First, we may be able to tie seemingly separate processes together, e.g., overt and covert orienting or spatial selective attention and spatial working memory. Secondly, we may be able to break down cognitive processes such as attention into somewhat separable physiological entities, e.g., shape vs. spatial selective attention. A reparsing of behavior based on underlying neurophysiological mechanisms could prove helpful in clinical diagnosis and the evaluation of medication efficacy, as well as in designing effective treatments for more carefully defined attentional dysfunctions.

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Impulsivity (cont'd from page 1)

screening mechanism. Over the last several decades, 'impulsive' individuals have repeatedly been shown to have abnormalities in event-related potentials that are consistent with this model.

Impulsivity may vary over time. Pharmacological manipulations or overstimulation could alter the balance between speed and context-checking, or could impair screening of responses. There are also times where the ability to suspend behavioral constraints may be adaptive.

There are two dominant animal models of impulsivity. The older is based on a ubiquitous property of behavior called reward discounting. For all species studied, the value of a delayed reward decreases as a hyperbolic function of time. Impulsivity is manifested by an exaggeration of this normal decrease. The tendency for an animal to prefer a small immediate reward over a larger delayed one is increased by serotonin depletion, by blockade of certain serotonergic receptors, or less consistently by stimulants, and is decreased by serotonin agonists.

The second model, called reflection-impulsivity, is based on inability to delay action until there is enough information to act successfully. An example is a procedure whereby a rat can choose between pressing two levers, one of which will result in delivery of food. There is a light over one of the levers, which initially is randomly placed but progressively favors the lever with food. After a rat has been trained in this procedure, stimulants or manipulations that deplete serotonin or block certain serotonin receptors increase the speed of responding, resulting in reduced accuracy, while manipulations that increase serotonergic transmission increase the accuracy of responding. These effects are not related to effects on attention or on motor speed.

The pharmacology of the two models of impulsivity is similar. It appears to involve a reciprocal relationship between dopaminergic, largely D2, and serotonergic, largely 5HT1B (at least in rodents) or 5HT2a, transmission. For example, serotonin depletion by dorsal raphe lesions produces an increase in 'impulsivity' that is prevented by D2 dopaminergic receptor blockade. Roles of norepinephrine, opiates, and amino acid systems are less well defined.

Impulsivity is considered an 'action-oriented' trait, like extraversion, novelty-seeking, or risk-taking. Impulsivity differs from these aspects of personality, however, because of its lack of association with any specific behavior. For example, memoirs of alpinists such as George Mallory or Sir Edmund Hillary reveal that, while they took staggering risks, they prepared for their feats as carefully as they could, leaving as little as possible to chance.

Personality scales, based on the above principles, measure impulsivity as a stable trait. The Barratt Impulsiveness Scale appears to have three factors: attentional impulsivity (including impatience with complexity), motor impulsivity, and nonplanning impulsivity. One might intuitively believe that impulsivity would be opposite to anxiety as a personality trait, but the Barratt Impulsiveness score is orthogonal to anxiety. Individuals who were high in impulsivity but low in anxiety were found to have antisocial traits, while those who were high in both were more likely to have severe psychiatric problems.

Human laboratory, or performance measures exist that correspond to both animal models of impulsivity. Reward-discounting impulsivity is measured by procedures where an individual can choose a small immediate or larger delayed reward. It is often designed so that the delay increases with successive choices of the delayed reward in order to determine the point at which the delayed reward is no longer selected. Personality disorders associated with impulsive behavior, and past histories of impulsive criminal behavior, are associated with increased selection of immediate rewards. This model has disadvantages in humans, however, because individuals can develop strategies to beat the system.

Reflection-impulsivity can be measured by a modification of the Continuous Performance Test developed by Donald M. Dougherty. In this procedure an individual is shown 5-digit numbers for 0.5 sec with 0.5 sec between numbers, and is instructed to respond when the index number reappears. The screen will either show the correct number, or a number where 4 of the 5 digits are correct, or a number with 5 random digits. In one variation of the test, there is a delay between the two numbers during which a distracter stimulus ('12345') is displayed three times at the same interval. Increased rates of commission errors, where the nearly-correct number is chosen, are associated with increased impulsivity. Possible confounds include roles of changes in attention or motivation. To some extent these can be accounted for by rates of correct and random responses.

IMPULSIVITY IN PSYCHIATRIC DISORDERS AND TREATMENT

Impulsive aggression is probably the most studied form of impulsive behavioral disturbance. Impulsive aggressive acts have three characteristics: 1) a low threshold for aggression, 2) inability to reflect on appropriateness or possible consequences, and 3) inability to modulate the response, leading to a maximal response that is out of proportion to the situation. Impulsive aggression differs from nonimpulsive aggression in being associated with abnormal event-related potentials (most often decreased p300 amplitude) and

response to lithium or certain anticonvulsants. Individuals with histories of impulsive aggression or impulsive criminal acts have high Barratt Impulsiveness scale scores and increased reflection-impulsivity. Other impulsive acts may share these characteristics with impulsive aggression.

Personality disorders, including borderline, antisocial, narcissistic, and histrionic personality disorders, are associated with prominent impulsive behavior, Barratt Impulsiveness scores, and both reflection-impulsivity and reward-discounting impulsivity on performance tests.

Substance abuse appears to have a two-way relationship to impulsivity. Stimulants generally increase impulsive behavior in animal models. Effects of stimulants in humans, however, may depend on pre-existing personality characteristics. Impulsivity may increase the risk of certain types of substance abuse. For example, alcoholism may fall into two major categories: an early-onset type associated with impulsive behavior and low serotonergic function, and a later-onset type without pre-existing prominent impulsive behavior.

Bipolar disorder is a lifelong disorder with recurrent depressive and/or manic episodes. Using observations of behavior during episodes and after their treatment, we have shown individuals with bipolar depression or mania to be more impulsive than controls even after successful treatment. Outpatients with bipolar disorder who were not in active episodes had substantially higher Barratt Impulsiveness scores than normal controls matched by age, gender, and education. Laboratory reflection-impulsivity correlated positively with manic symptoms.

Suicide is the cause of death in about 15% of those with bipolar disorder, 10% with schizophrenia or with recurrent major depression, and is the third leading cause of death in adolescents and young adults. Risk of suicide is not predicted by severity of depression alone but by a combination of hopelessness and impulsivity. Suicide attempts vary in their degree of impulsivity. Predominately impulsive suicide attempts are dangerous because of 1) the lack of warning or evidence for planning, 2) apparently trivial precipitants, and 3) use of methods whose lethality is out of proportion to the apparent intent of the attempter.

Behavioral treatments for impulsivity require the development of compensations for the lack of the internal behavioral filter that is thought to underlie impulsivity. This can involve learning to recognize the situations in which impulsive behavior is likely to occur and developing strategies to avoid or defuse them, learning to recognize affects associated with impulsive behavior, and learning to develop practical problem-solving methods. Specific examples include relapse-prevention

strategies in substance use disorders, anger management, and dialectic behavior therapy in personality disorders.

Pharmacological treatments include lithium and certain anticonvulsants. Lithium was found to be effective in impulsive aggression in the late 1960's. Impulsively aggressive individuals successfully treated with lithium reported that while they still had a low threshold for aggressive behavior, they had a split second in which they could reflect on whether an aggressive response was actually appropriate. They noted that, unlike treatment with sedatives or antipsychotic medicines, when treated with lithium they could still defend themselves. Similarly, a person successfully treated with the anticonvulsant valproic acid stated "they always said to count to ten if I got mad. Before the study I couldn't get to one but now I can count to 3 or 4."

CONCLUSIONS

Impulsivity is central to the balance between initiation and inhibition of behavior. This overview has presented impulsivity as if it were a single construct, which is a large and somewhat impulsive oversimplification. Studies comparing models of impulsivity and investigating impulsivity in different contexts show it to be multifactorial, with personality, performance, and neurophysiologic measures revealing related but partially distinct phenomena. Animal models of impulsivity will eventually shed light on basic aspects of its physiology, including adaptive properties over time, relationship to other aspects of motivation and reward systems, and genetics. These models are still in a relatively early stage of development.

Clinically, the measurement of impulsivity and its use in diagnosis, prediction of response to treatment, and monitoring of treatment or course of illness is still at an early stage. Neurophysiologic measures are tantalizing but nonspecific and have been little-used outside of impulsive aggression. The apparently different temporal properties of personality and laboratory impulsivity in bipolar disorder is preliminary and its generalizability is not yet established.

The current diagnostic system in psychiatry is based on descriptive and nonspecific syndromes like depression, mania, and psychosis. Understanding of more basic behavioral entities, like impulsivity, may be the beginning of a more physiologically based system of diagnosis and treatment.

About the Authors: Sereno and Swann

Anne Sereno completed her undergraduate studies in Mathematics and Biological Sciences at Northern Illinois University in DeKalb, Illinois and earned her Ph.D. in

Psychology from Harvard University, Cambridge, MA. Dr. Sereno began her postdoctoral training at Harvard and completed her postdoctoral work at Baylor College of Medicine in Houston, in the laboratory of Dr. John Maunsell. In 1995, she accepted a position as Assistant Professor at Rutgers University in Newark, NJ. Dr. Sereno returned to Houston in 1999 to accept a faculty position in the Department of Neurobiology and Anatomy at UT-Houston.

Alan Swann completed his undergraduate training in chemistry at the University of Manchester, England and Tulane University in Louisiana. He attended medical school at UT Southwestern in Dallas, earning his M.D. in 1972. His postgraduate work included training in both the clinical and basic research areas. Following a two-year residency at Columbia Presbyterian Hospital in New York, Dr. Swann worked at the NIH/NINDS as a research associate in the Laboratory of Neurochemistry. He finished his postgraduate training at Yale University, completing both a residency and research fellowship in Psychiatry. In 1980, Dr. Swann moved to Houston to accept a position in the Department of Psychiatry and Behavioral Sciences of UT-Houston as an assistant professor. He moved through the ranks to become Professor and Vice Chairman for Research in the Department of Psychiatry and Behavioral Sciences, and of the Graduate School of Biomedical Sciences. He holds the Pat R. Rutherford, Jr. Chair in Psychiatry. He is also an attending physician at Memorial Hermann Hospital and at the Harris County Psychiatric Center.

Graduate and Postdoctoral Training

For information concerning graduate and postdoctoral training at UT-Houston, contact Dr. Jack Waymire at 713-500-5620 or jack.c.waymire@uth.tmc.edu



FROM THE DIRECTOR

Brain Awareness Week 2001: Public Outreach

The University of Texas Health Science Center at Houston participates annually in Brain Awareness Week (BAW), an international campaign orchestrated by the Dana Alliance for Brain Initiatives to promote the public and personal benefits of brain research. For six years, The Neuroscience Research Center (NRC) has organized and hosted the public outreach events that represent the University's participation in the annual BAW campaign. In March of this year, UT-Houston offered several exciting BAW activities to Houstonians, including two public forum sessions, a brain display at a local library, and two new Partners in Education events. Each event was tailored to a specific age group and all were successful in promoting neuroscience research.

The two public forum sessions were for many years the sole BAW activity of UT-Houston and designed for an adult audience. Attendees are provided the unique opportunity to learn about neuroscience research and related issues through lectures by and conversations with scientists, clinicians, and representatives of local support groups. Each year, the public forum sessions have grown in size and attendance.

With the addition of new BAW activities at UT-Houston came a new focus on a young audience. For Brain Awareness Week 2001, the NRC sponsored a month-long display featuring the brain at the First Colony public library. Throughout the month of March, the display housed various models and illustrations of the brain, skull, neuron, and synapse that included captions written at a child's level of understanding. The exhibit was complete with real human

Neurofax

The NRC publishes a monthly calendar of events (*Neurofax*) identifying the ongoing research activities at UT-Houston and other institutions in the Texas Medical Center. Announcements of seminars, grand rounds, research colloquia, symposia and conferences are included. *Neurofax* is the only publication of its kind containing information concerning neuroscience-related lectures of the Texas Medical Center (TMC) compiled on a monthly basis. Published in all months, except August, *Neurofax* is distributed in hardcopy and E-mail form to members of the NRC, as well as to individuals and departments at other institutions in the TMC and in the Houston area. It is also available and updated weekly on the Web (<http://nba19.med.uth.tmc.edu/nrc/neurofax/current.html>). If you would like to advertise an upcoming neuroscience-related lecture in the *Neurofax*, or if you would like to be placed on our mailing list, please contact Marijane de Tranaltes at Marijane.DeTranaltes@uth.tmc.edu.

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NRC Fall 2001 Distinguished Lecturer

Solomon H. Snyder, M.D.

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Johns Hopkins University School of Medicine
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Solomon Snyder, M.D. will be the Fall 2001 Distinguished Lecturer in the University of Texas-Houston Neuroscience Research Center's Distinguished Lectureship Series. Dr. Snyder earned his M.D. from Georgetown Medical School in Washington, D.C. He received research training at the National Institute of Mental Health, NIH, in Bethesda, MD, followed by residency training in the Department of Psychiatry at the Johns Hopkins Hospital in Baltimore, MD. In 1966, Dr. Snyder began his career at the Johns Hopkins University School of Medicine as Assistant Professor of Pharmacology and Experimental Therapeutics. He rose through the ranks to become Director of the Department of Neuroscience and Distinguished Service Professor of Neuroscience, Pharmacology, and Psychiatry; appointments he holds today.

On Thursday, September 20, 2001 Dr. Snyder will visit the University of Texas-Houston and present his lecture entitled "Novel Neural Messengers." The lecture will begin at 4:00 p.m. in MSB 3.001 in the University of Texas-Houston Medical School Building. For more information, contact the NRC at 713-500-5540 or nba-nrc@uth.tmc.edu