

ATTENTION AS AN ORGAN SYSTEM

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ABSTRACT

In recent years it has been possible to examine selective attention as an organ system with its own functional anatomy, circuitry and cellular structure. Although information remains incomplete on each of these levels, this view has already altered our knowledge concerning many perplexing problems in cognitive science and allowed important insights into neurological and psychiatric disorders of children and of adults. It promises to help describe the evolutionary and developmental basis of a principle brain mechanism of voluntary control, thus advancing the way toward an understanding of how genetics and culture shape control systems. While all humans have an attention system, the efficiency of its operation clearly differs between people. These differences serve as a basis for differences both in intelligence and in emotional control.

1. Introduction

Attention is relatively easy to define subjectively as in the classical definition of William James who said:

“Everyone knows what attention is. It is the taking possession of the mind in clear and vivid form of one out of what seem several simultaneous objects or trains of thought.” (James, 1890).

However, this subjective definition does not provide hints that might lead to an understanding of attentional development or pathologies. The theme of our paper is that it is now possible to view attention much more concretely as an organ system. We follow the dictionary definition of an organ system (Webster’s dictionary).

“An organ system may be defined as differentiated structures in animals and plants made up of various cell and tissues and adapted for the performance of some specific function and grouped with other structures into a system”.

We believe that viewing attention as an organ system aids in answering many perplexing issues raised in cognitive psychology, psychiatry and neurology. Neuroimaging studies have systemically shown that a wide variety of cognitive tasks can be seen as activating a distributed set of neural areas, each of which can be identified with specific mental operations (Posner & Raichle, 1994; 1998). Perhaps the areas of activation have been more consistent for the study of attention than for any other cognitive system. We can view attention as involving specialized networks to carry out functions such as achieving and maintaining the alert state, orienting to sensory events and controlling thoughts and feelings.

Part 2 of this chapter examines the functional anatomy of the network involved in alerting and orienting to sensory events. Orienting to sensory events provides an important model for the study of attention. Part 3 considers attention in the sense of exercising voluntary control over thoughts, feelings and actions. In this section we examine a frontal network involved in this form of cognitive and emotional control. Next we consider the development of attentional networks in normal individuals. The final two sections consider the impact of viewing attention as an organ system and on questions in cognition and neuropsychology.

2. Orienting to Sensory Events

The vast majority of studies on attention have involved orienting to sensory events, particularly visual events. The findings of these studies provide the basis for our limited understanding of how to approach brain mechanisms of attention. In this field a basic distinction is between those brain areas which are influenced by acts of orienting (*sites*) and those which are parts of the orienting network itself, thus the *sources* of the orienting

influence (See Figure 1). Although our discussion is limited to vision we believe that the sources of the attention effect are similar in other modalities (Macaluso, Frith & Driver, 2000).

INSERT FIGURE 1

Sites and Sources

Normally all sensory events act both to contribute to a state of alertness and to orient attention. In order to distinguish the brain areas that are involved in orienting from the sites at which they operate it is useful to separate the presentation of a cue indicating where a target will occur from the presentation of the target requiring a response (Posner, 1978; Corbetta et al 2000). This methodology has been used for behavioral studies with normal people (Posner, 1978) patients (Posner et al, 1994), monkeys (Marrocco & Davidson, 1998) and in studies using scalp electrical recording and event related neuroimaging (Heinze, et al, 1994). A recent version of the cueing approach embedded in the attention network test (ANT) is shown in Figure 2. Two types of cues are of interest. Some cues provide information on when the target will occur. These warning signals lead to changes in a network of brain areas related to alerting. Other cues provide information on aspects of the target such as where it will occur and lead to changes in the orienting network.

INSERT FIGURE 2

Studies using event related fMRI have shown that following the presentation of the cue and before the target is presented, a network of brain areas become active (Corbetta, et al, 2000; Kastner, et al, 1999). There is widespread agreement about the identity of these areas but there remains a considerable amount of work to do in order to understand the function of each area.

When a target is presented in isolation at the cued location it is processed more efficiently than if no cue had been presented. The brain areas influenced by orienting will be those that would normally be used to process the target. For example, in the visual system orienting can influence sites of processing in the primary visual cortex, or in a variety of extra striate visual areas where the computations related to the target are performed. Orienting to target motion influences area MT (V5) while orienting to target color will influence area V4 (Corbetta, et al, 1991). This principle of activation of brain areas also extends to higher-level visual input as well. For example, attention to faces modifies activity in the face sensitive area of the fusiform gyrus (Wojciulik, et al, 1998). The finding that attention can modify activity in primary visual areas (Posner & Gilbert, 1999) has been of particular importance because this brain area has been more extensively studied than any other.

When multiple targets are presented they tend to suppress the normal level of activity which they would have produced if presented in isolation (Kastner, et al, 1999). One

important role of orienting to a particular location is to provide a relative enhancement of the target at that location in comparison with other items presented in the visual field.

Functional Anatomy

Work with stroke patients shows that lesions of many brain areas result in difficulty shifting attention to locations or objects that were conveyed directly to the damaged hemisphere (Rafal, 1998). In neurology these patients would be said to be suffering from extinction. Experimental studies suggested that we could define different forms of extinction due to lesions of the parietal lobe, the midbrain or the thalamus (Posner, 1988) (see Figure 3). These results suggest that lesions to different areas produce a loss of particular mental operations. By mental operation it is meant a component or subroutine of an overall act. For example, in order to shift attention to a new object one first has to disengage attention from its current focus and move it to the new location where the target can be engaged. Data in the 1980s suggested that operations of disengage (parietal lobe), move (superior colliculus) and engage (pulvinar) were computed in different brain areas that formed a vertical network that together performed the task of orienting. The idea of localization of mental operations in separate brain areas was appealing because it suggested a solution to the old problem of how there could be localization when widely separated damage could produce the same general behavioral effect (e.g. extinction). It suggested that to perform an integrated task the brain had to orchestrate a distributed network of brain areas, yet the computations underlying a single mental operation were local.

INSERT FIGURE 3

More recent studies involving both patients and imaging seem to support this general approach to localization, but suggest somewhat different separation of the operations involved. As new methods of neuroimaging have become available they have been applied to the problem of orienting to sensory (often visual input). The results have helped to clarify how operations are localized. A paradox of the lesions studies in the early 1980s was that the superior parietal lobe seemed to be the area most related to producing a difficulty in disengaging from a current focus of attention. Yet most clinical data seemed to support the idea that clinical extinction arose from more inferior lesions in the temporal-parietal junction and/or superior temporal lobe.

Event related imaging studies have served to reconcile this difference. There seem to be two separate regions, both of which can both produce difficulty in shifting attention in contralateral space, but for quite different reasons. Lesions of the temporal-parietal junction or superior temporal lobe are important when a novel or unexpected stimulus occurs (Friedrich, et al, 1998; Karnath, Ferber & Himmelbach, 2001). When functioning normally, this area allows disengaging from a current focus of attention to shift to the new event. This area is most critical in producing the core elements of the syndrome of neglect or extinction in both humans and monkeys although the exact location of the most critical area may differ between the two species. In addition, there is much clinical evidence that

in the human there is lateralization in that the right temporal parietal junction may be more important to the deficit than the left (Mesulam, 1981; Perry & Zeki, 2000).

A different region, the superior parietal lobe, seems to be critical for voluntary shifts of attention following the cue. In one event related fMRI study this region was active following a cue informing the person to shift attention covertly (without eye movement) to the target (Corbetta, et al, 2000). The region is part of a larger network that includes frontal eye fields and the superior colliculus that appears to orchestrate both covert shift of attention and eye movements toward targets (Corbetta, 1998). When people voluntarily move their attention from location to location while searching for a visual target this brain area is also active.

There is evidence from other patient groups indicating brain areas involved in shifting attention. For example, patients with Alzheimer's disease involving degeneration in the superior parietal lobe have difficulty in dealing with central cues that inform them to shift their attention (Parasurman, et al, 1992). There is also evidence that lesions of the superior colliculus may be involved in the preference for novel locations rather than locations to which one has already oriented (Sapir, et al, 1999). Patients with lesions of the thalamus (most likely the pulvinar) also show subtle deficits in visual orienting tasks that may be related to the access of the ventral information-processing stream. It seems that a vertical network of brain areas related to voluntary eye movements and to processing novel input are critical elements of orienting, but a precise model including a role for all of these areas is still lacking.

The methods of neuroimaging have proven critical to testing the general proposition that mental operations involved in a given task were widely distributed among brain areas (Posner & Raichle, 1996). In fact, the very first papers using positron emission tomography suggested that visual and auditory words were analyzed by a distributed network of brain areas, each of which performed an operation (Posner, et al, 1988). In the fifteen years since that time studies have shown that many tasks produce networks of widely spaced activation that most often were interpreted as carrying out particular operations.

It is likely that we still do not have the final answer as to the exact operations that occur at each location even in a relatively simple act like shifting attention to a novel event. Nonetheless, the imaging data provide reconciliation between clinical observations and imaging studies. The results of attentional studies, as with many other areas of cognition, support the general idea of localization of component operations.

Transmitters

It is very important to be able to link the neurosystem results, that suggest brain areas related to attention, with cellular and synaptic studies that provide more details as to the local computations. One strategy for doing so is to study the pharmacology of each of the attention networks. To carry out these tests it is important to be able to study monkeys who are able to use cues to direct attention to targets. Fortunately cueing studies can be run successfully in monkeys.

A series of pharmacological studies with alert monkeys have related each of the attentional networks we have discussed with specific chemical neuromodulators (Davidson & Marrocco, 2000; Marrocco & Davidson, 1998). Alerting is thought to involve the cortical distribution of the brain's norepinephrine (NE) system arising in the locus coeruleus of the midbrain. Drugs like clonidine and guanfacine act to block NE, reduce or eliminate the normal effect of warning signals on reaction time, but have no influence on orienting to the target location (Marrocco & Davidson, 1998).

Cholinergic systems arising in the basal forebrain play a critical role in orienting. Lesions of the basal forebrain in monkeys interfere with orienting attention (Voytko, et al, 1994). However, it does not appear that the site of this effect is in the basal forebrain. Instead it appears to involve the superior parietal lobe. Injections of scopolamine directly into the lateral intraparietal area of monkeys, a brain area containing cells which are influenced by cues about spatial location, have been shown to have a large effect on the ability to shift attention to a target. Systemic injections of scopolamine have a smaller effect on covert orienting of attention than do local injections in the parietal area. Cholinergic drugs do not affect the ability of a warning signal to improve performance and thus appears to be a double dissociation that relates NE to the alerting network and Ach (acetylcholine) to the orienting network. These observations in the monkey have also been confirmed by similar studies in the rat (Everitt & Robbins, 1997). Of special significance in the rat, comparisons of the cholinergic and dopaminergic mechanisms have shown that only the former influence the orienting response (Everitt & Robbins, 1997; Stewart, Burke & Marrocco, 2001).

The evidence relating Ach to the orienting network and NE to the alerting network provides strong evidence of dissociation between the different attentional networks. In the next section we show that the frontal executive network is closely related to dopamine as a neural modulator.

3. Executive Network

Executive control is most needed in situations, which involve planning or decision-making, error detection, novel responses, and in overcoming habitual actions. While these concepts are somewhat vague a more explicit version of the idea of executive attention has recently been developed which stresses the role of attention in monitoring and resolving conflict between computations occurring in different brain areas (Botwinick, et al, 2001). While this view may not be adequate to explain all of the existing data, it provides a useful model for summarizing much of what is known.

Functional Anatomy

A very large number of functional imaging studies have examined tasks that involve executive attention. These "thinking" tasks often activate a wide range of frontal and often posterior areas. Moreover, manipulations of the content of material have often shown that the same areas may be active irrespective of whether the stimuli are spatial, verbal or

visual objects. This has led some to conclude that the frontal lobes may be an exception to the specific identification of brain areas with mental operations that we have discussed for orienting (Duncan and Owen, 2000; Goldberg, 2001).

A frontal network including the anterior cingulate and lateral prefrontal cortex has been active in different tasks that involve attention when conflict is present and producing a non habitual response is required. One important study (Duncan, et al, 2001) examined a wide range of verbal, spatial and object tasks selected from intelligence tests that had in common a strong loading on the factor of general intelligence (g). These items were contrasted with perceptually similar control items that did not require the kind of attention and thought involved in general intelligence. This subtraction led to differential activity in two major areas. One was the anterior cingulate and the second was lateral prefrontal cortex.

Many imaging studies have been conducted using either the Stroop task or variants of it that involved conflict among elements (Bush, Luu & Posner, 2000). The Stroop task requires the person to respond to the color of ink (e.g. red) when the target is a competing color word (e.g. blue). Another frequently used conflict task is the target tasks illustrated in Figure 2. In this flanker task (Ericksen & Ericksen, 1974) the person is required to respond to a central stimulus (e.g. an arrow pointing left) when it is surrounded by flankers that either point in the same direction (congruent) or in the opposite direction (incongruent). [Should the spatial conflict task be mentioned here ???] Recently, we examined three conflict tasks using the same subjects and scanner to determine areas of activation (Fan, et al, 2001). We found that all three tasks activated areas of the anterior cingulate some of which were unique, but had a common focus (See Figure 4). In addition, all activated some areas of the prefrontal cortex, but those areas appeared to differ between tasks.

INSERT FIGURE 4

An event related functional MRI study of the Stroop effect used cues to separate presentation of the task instruction from reaction to the target (McDonald, et al, 2000). Lateral prefrontal areas were responsive to cues indicating whether the task involved naming the word or dealing with the ink color. The cue did not activate the cingulate. When the task involved naming the ink color the cingulate was more active on incongruent than congruent trials. This result reflects the general finding that lateral areas are involved in representing specific information over time (working memory), while medial areas are more related to the detection of conflict.

Another cue to the functional activity in these areas comes from studies of generating the use of a word. In a typical version of this task, subjects are shown a series of forty simple nouns (e.g. hammer) (Raichle, et al, 1994). In the experimental condition they indicate the use of each noun (for example, hammer -> pound). In the control condition, they simply read the word aloud. The difference in activation between the two tasks illustrates what happens in the brain when subjects are required to develop a very simple thought, in this case how to use a hammer. Results illustrate that the anatomy of this high-

level cognitive activity is similar enough among individuals to produce focal average activations that are both statistically significant and reproducible.

One area that is more strongly activated when generating the use of a word is on the midline of the frontal lobe in the anterior cingulate gyrus. Two additional areas of cortical activation that are more active in the generate condition are in the left lateral prefrontal cortex and posterior temporal cortex. Both of these areas have been shown to be involved in many tasks dealing with processing the meaning of words or sentences.

Circuitry

To examine the time course of these activations it is possible to use a large number of scalp electrodes to obtain scalp signatures of the generators found active in imaging studies (Abdullaev & Posner, 1998). When subjects obtain the use of a noun, there is an area of positive electrical activity over frontal electrodes starting about 150 msec after the word appears. This early electrical activity is generated by the large area of activation in the anterior cingulate.

A left prefrontal area (anterior to and overlapping classical Broca's area) begins to show activity about 200 msec after the word occurs. In our initial data we identified this area with semantic processing because it was active in tasks such as classifying the word into categories, obtaining an association or treating one type of word (e.g. animal names) as a target, but not in reading words aloud. These empirical findings have proven to be true in much subsequent work (for a review see Abdullaev & Posner, 1998). However, the finding that frontal areas appear involved in working memory and the finding that the time course of the activation of the lateral frontal area was early both make it likely that this lateral frontal area is related to operations such as holding the lexical item in a brief store during the time needed to which to look up the associated word use. The left posterior brain area found to be more active during the processing of the meaning of visual words did not appear until a much later time (500 msec). This activity is near the classical Wernicke's area; lesions of which are known to produce a loss of understanding of meaningful speech. We found evidence of the transfer of information from left frontal electrodes to the posterior area at about 450 millisecond into the task. Since the response time for this task was about 1,100 msec this would leave time for the generation of related associations needed to solve the task.

Practice on a single list of words reduces the activation in the cingulate and lateral cortical areas (Raichle, et al 1994). Thus the very same task, when it is highly over learned, avoids the circuits involved in thought and relies upon an entirely different circuitry.

These studies provide a start in understanding the functional roles of different brain areas in carrying out executive control. The medial frontal area appears most related to the executive attention network and is active when there is conflict among stimuli and responses. It may be serving as a monitor of conflict, but it is possible that it plays other roles as well. The lateral prefrontal area seems to be important in holding in mind the information relevant to the task. Even when a single item is presented, it may still be

necessary to hold it in some temporary area while other brain areas retrieve information relevant to the response. Together these two areas are needed to solve nearly any problem, which depends upon retrieval of stored information. Both of these areas could be said to be related to attention, or one might identify only the medial area with attention and the lateral one with working memory. In either case they begin to give us a handle on how the brain parses high-level tasks into individual operations that are carried out in separate parts of the network.

Lesion Studies

Classical studies of strokes of the frontal midline including the anterior cingulate showed a pervasive deficit of voluntary behavior (Damasio, 1994; Kennard, 1955). Patients with akinetic mutism can orient to external stimuli and follow people with their eyes, but they do not initiate voluntary activity. Recent studies of patients with small lesions of the anterior cingulate (Ochsner, et al, 2001; Turken & Swick, 1999) show deficits in conflict related tasks, but these patients frequently recover from their deficits suggesting that other areas may also be involved. In some cases lesions of the mid frontal area in children and adults may produce permanent loss of future planning and appropriate social behavior (Damasio, 1994). Early-childhood damage in this area can produce permanent deficits in decision-making tasks that require responses based on future planning (Anderson, et al, 2000).

Cellular Mechanisms

The anterior cingulate and lateral frontal cortex are target areas of the ventral tegmental dopamine system. All of the dopamine receptors are expressed in layer five of the cingulate.

The association of the anterior cingulate with high-level attentional control may seem rather odd because this is clearly a phylogenetically old area of the brain. Although the anterior cingulate is an ancient structure, there is evidence that it has evolved significantly in primates. Humans and great apes appear to have a unique cell type found mainly in layer V of the anterior cingulate and insula, a cell type not present in other primates (Nimchinsky et al., 1999). These cells also undergo a rather late development in line with the findings that executive control systems develop strongly during later childhood (Allman, et al, 2001)(see also next section). Although the precise function of this cell is not known, high correlations between its volume and encephalization suggest a likely role in higher cortical functioning. The proximity of these cells to vocalization areas in primates led Nimchinsky and colleagues to speculate that these cells may link emotional and motor areas, ultimately resulting in vocalizations that convey emotional meaning. Although there is as yet no direct evidence linking the cellular architecture of the anterior cingulate to cingulate activity detected during neuroimaging studies, the importance of this area for emotional and cognitive processing (Busch et al, 2000) makes further exploration compelling.

Several replicated human genetic studies demonstrate an association of one of the dopamine receptor genes D4 (DRD4) located on chromosome 11p15.5 and an attentional disorder common in childhood (attention deficit/hyperactivity disorder or ADHD). About 50% of the ADHD cases have a 7-repeat allele whereas only about 20% ethnically matched control subjects have a 7-repeat allele. However, a direct comparison of children with ADHD who either have or do not have the 7 repeat allele suggest that attentional abnormalities are more common in those children without the 7 repeat (Swanson, et al, 2000). The authors suggest that there are different routes to ADHD only some of which involve a specific reduction in cognitive ability.

The anterior cingulate is strongly activated by a wide variety of tasks that create conflict between elements (Bush, et al, 1998). For example, if people are asked to respond to the number of items in the visual field and the items are digits whose name differs from the number of objects present, conflict exists between the digit name and the desired numerical response. This counting Stroop task, like many other conflict tasks studied by neuroimaging, produces activation of the anterior cingulate (Bush, et al, 1998). Adult subjects who suffer from ADHD have been studied in the numerical Stroop. While they perform only slightly worse than normal persons they appear to activate an entirely different network of brain areas than do the normals. Where normals activate the anterior cingulate the ADHD adults seem to rely on the anterior insula, which is usually associated with responses in more routine tasks not involving conflict (Bush et al 1999). The insula is active when reading words but not in generating new uses unless they are well practiced, thus this area may represent a more primitive pathway allowing for less effortful control over the task.

Washburn (1998) demonstrated the effects of conflict in Rhesus monkey by first training them to appreciate the quantity of a digit by pairing digits with appropriate amounts of reward. The monkeys were then asked to indicate which of two displays contained the larger number of items. When the items were digits the number in the display could either be congruent (larger number of objects was also the larger digit) or incongruent (smaller number of objects was the larger digit). Monkeys performed this task and showed greater difficulty in errors and RT in the incongruent condition. Moreover, despite hundreds of trials at the task monkeys continued to produce many more errors on incongruent trials than do humans. Monkeys appeared to have a reduced capacity to avoid interference despite extensive training.

Washburn and his associates noticed that mastery of complex tasks, such as the Stroop by Rhesus monkeys, led to a reduction of aggression and an improvement in their social behavior. They suggested that the Rhesus monkey might serve as a model of ADHD in humans. The existence of animals' models for the Stroop (Washburn, 1998) opens up the possibility of cellular studies for examining the role of the cingulate in attention.

Schizophrenia is another disorder that produces a disruption of attentional control in addition to other emotional and cognitive problems. Benes (1999) reports subtle abnormalities of the anterior cingulate in post mortem analyses of schizophrenic brains. She argues that schizophrenic brains may be dysfunctional due to a shift in dopamine

regulation from pyramidal to non-pyramidal cells. These effects involve the D2 receptor and are strongest within layer II of the anterior cingulate. Her theory provides a possible cellular level explanation for anterior cingulate dysfunction in a second abnormality noted for its attentional deficits.

In this section we have examined imaging, cellular and genetic studies that illustrate the physical basis of the executive attention network. While attention deficit disorder and schizophrenia are striking examples of pathologies related to this network it is clear that attention also differs between normal individuals. The next section examines studies on this topic. While attention deficit disorder and schizophrenia are striking examples of pathologies related to attention, it is clear that attention differs between normal individuals. The next section examines studies on this topic.

4. Individual Differences

Almost all studies of attention have been concerned with either the general abilities involved or with the effects of brain injury or pathology on attention. However, it is clear that normal individuals differ in their ability to attend to sensory events and even more clearly in their ability to concentrate for long periods on internal trains of thought.

To study these individual differences we have developed an attention networks test (see Figure 2) that examines the efficiency of the three brain networks we have described (Fan et al, in press). We used reaction times derived from the task shown in Figure 2 to make subtractions shown in Figure 5. The data provide three numbers that represent the skill of each individual in the alerting, orienting and executive networks. In a sample of 40 normal persons we found each of these numbers to be reliable over repeated presentations. In addition, we found no correlation among the numbers. An analysis of the reaction times found in this task show large main effects for cueing and for the type of target. There were only two small interactions indicating some lack of independence among the networks. One of these interactions was that orienting to the correct target location tended to reduce the influence of the surrounding flankers shown. In addition, omitting a cue, which produces relatively long reaction times, also reduces the size of the flanker interference. Presumably this is because some of the conflict is reduced during the time the subject is preparing to process the target location.

INSERT FIGURE 5

The ability to measure differences in attention among adults raises the question of the degree to which attention is heritable. In order to deal with this issue we used our attention network test to study 26 pairs of monozygotic and 26 pairs of dizygotic same sex twins (Fan, et al, submitted). We found strong correlations between the monozygotic twins for both the executive and alerting networks. For the alerting network we found a similar although somewhat smaller correlation among the dizygotic twins, but for the executive network the dizygotic twins were only slightly correlated. This lead to an estimate of heritability of the executive network of .89. Because of the small sample the estimate of 95

percent confidence interval for heritability is between .3 and .9. Nonetheless these data support a role for genes in the executive and possibly in the alerting network.

We have used the association of the alerting and executive network with the neuromodulators NE and DA as a way of searching for candidate genes that might relate to the efficiency of these networks (Fossella, et al, in process). To do this we have so far run 100 persons in the ANT and taken bucal swabs to examine frequent polymorphisms in genes related to their respective neuromodulators. So far we have obtained preliminary evidence of the association of the DRD4 and MAOA gene alone or in combination with the executive network and in the case of DRD4 the overall reaction time. We have also seen some relation of MAOA and COMT with the alerting network. At this time we are continuing the search both in normal subjects and in patient populations for which abnormalities may be in attentional networks.

5. Development of Attentional Networks

A major advantage of viewing attention as an organ system is to trace the ability of children and adults to regulate their thoughts and feelings. Over the first few years of life the regulation of emotion is a major issue of development. Panksepp (1998) lays out anatomical reasons why the regulation of emotion may pose a difficult problem for the child as follows:

"One can ask whether the downward cognitive controls or the upward emotional controls are stronger. If one looks at the question anatomically and neurochemically the evidence seems overwhelming. The upward controls are more abundant and electrophysiologically more insistent: hence one might expect they would prevail if push came to shove. Of course, with the increasing influence of cortical functions as humans develop, along with the pressures for social conformity, the influences of the cognitive forces increase steadily during maturation. We can eventually experience emotion without sharing them with others. We can easily put on false faces, which can make the facial analysis of emotions in real-life situations a remarkably troublesome business." (Panksepp, 1998, 319).

The ability of attention to control distress can be traced to early infancy (Harmon, Rothbart & Posner, 1997). In infants as young as three months we have found that orienting to a visual stimulus provided by the experimenter, produces powerful if temporary soothing of distress. One of the major accomplishments of the first few years is for infants to develop the means to achieve this regulation on their own.

An early sign of the control of cognitive conflict is found in the first year of life. For example, in A-not-B tasks, children are trained to reach for a hidden object at location A, and then tested on their ability to search for the hidden object at a new location B. Children younger than 12 months of age tend to look in the previous location A, even though they see the object disappear behind location B. After the first year, children develop the ability to inhibit the prepotent response toward the trained location A, and successfully reach for the

new location B (Diamond, 1991). During this period, infants develop the ability to resolve conflict between line of sight and line of reach when retrieving an object. At nine months of age, line of sight dominates completely. If the open side of a box is not in line with the side in view, infants will withdraw their hand and reach directly along the line of sight, striking the closed side (Diamond, 1991). In contrast, 12-month-old infants can simultaneously look at a closed side while reaching through the open end to retrieve a toy.

The ability to use context to reduce conflict can be traced developmentally using the learning of sequences of locations. Infants as young as 4 months can learn to anticipate the location of a stimulus provided the association in the sequence are unambiguous. In unambiguous sequences each location is invariably associated with another location (e.g. 123) (Clohessy, Posner & Rothbart, 2001). Because the location of the current target is fully determined by the preceding item, there is only one type of information that needs to be attended and therefore no conflict (e.g. location 3 always follows location 2). Adults can learn unambiguous sequences of spatial locations implicitly even when attention is distracted by a secondary task (Curran & Keele, 1993).

Ambiguous sequences (e.g., 1213) require attention to the current association and in addition to the context in which the association occurs (e.g., location 1 may be followed by location 2, or by location 3). Ambiguous sequences pose conflict because for any association there exist two strong candidates that can only be disambiguated by context. When distracted, adults are unable to learn both ambiguous sequences of length six (e.g. 123213) (Curran & Keele, 1993), a finding that demonstrates the need for higher-level attentional resources to resolve this conflict. Even simple ambiguous associations (e.g. 1213) were not learned by infants until about two years of age (Clohessy, et al., 2001).

Developmental changes in executive attention were found during the third year of life using a conflict task (Gerardi-Caulton, 2001). Because children of this age do not read, location and identity rather than word meaning and ink color served as the dimensions of conflict (spatial conflict task). Children sat in front of two response keys, one located to the child's left and one to the right. Each key displayed a picture, and on every trial a picture identical to one of the pair appeared on either the left or right side of the screen. Children were rewarded for responding to the identity of the stimulus, regardless of its spatial compatibility with the matching response key (Gerardi-Caulton, 2000). Reduced accuracy and slowed reaction times for spatially incompatible relative to spatially compatible trials reflect the effort required to resist the prepotent response and resolve conflict between these two competing dimensions. Performance on this task produced a clear interference effect in adults and activated the anterior cingulate (see Figure 4). Children 24 months of age tended to fix on a single response, while 36-month-old children perform at high accuracy levels, but like adults responded more slowly and with reduced accuracy to incompatible trials.

At 30 months, when toddlers were first able to successfully perform the spatial conflict task, we found that performance on this task was significantly correlated with the same toddlers' ability to learn the ambiguous associations in the sequence learning task described above (Rothbart, Ellis & Posner, in process). This finding, together with the

failure of 4-month-olds to learn ambiguous sequences, holds out the promise of being able to trace the emergence of executive attention during the first years of life.

The importance of being able to study the emergence of executive attention is enhanced because cognitive measures of conflict resolution in these laboratory tasks have been linked to aspects of children's self control in naturalistic settings. Children relatively less affected by spatial conflict also received higher parental ratings of temperamental effortful control and higher scores on laboratory measures of inhibitory control (Gerardi-Caulton, 2000).

Questionnaires have shown the effortful control factor, defined in terms of scales measuring attentional focusing, inhibitory control, low intensity pleasure, and perceptual sensitivity (Rothbart, et al, in press) to be inversely related to negative affect. This relation is in keeping with the notion that attentional skill may help attenuate negative affect, while also serving to constrain impulsive approach tendencies.

Empathy is also strongly related to effortful control, with children high in effortful control showing greater empathy. To display empathy towards others requires that we interpret their signals of distress or pleasure. Imaging work in normals shows that sad faces activate the amygdala. As sadness increases, this activation is accompanied by activity in the anterior cingulate as part of the attention network (Blair, Morris, Frith, Perrett & Dolan, 1999). It seems likely that the cingulate activity represents the basis for our attention to the distress of others.

Developmental studies find the two routes to successful socialization. A strongly reactive amygdala would provide the signals of distress that would easily allow empathic feelings toward others. These children are relatively easy to socialize. In the absence of this form of control the development of the cingulate would allow appropriate attention to what signals are provided by amygdala activity. Consistent with its influence on empathy, effortful control also appears to play a role in the development of conscience. The internalization of moral principles appears to be facilitated in fearful preschool-aged children, especially when their mothers use gentle discipline (Kochanska, 1995). In addition, internalized control is facilitated in children high in effortful control (Kochanska, et al, 1996). Two separable control systems, one reactive (fear) and one self-regulative (effortful control) appear to regulate the development of conscience.

Individual differences in effortful control are also related to some aspects of metacognitive knowledge, such as theory of mind (i.e., knowing that people's behavior is guided by their beliefs, desires, and other mental states) (Carlson & Moses, 2001). Moreover, tasks that require the inhibition of a prepotent response correlate with theory of mind tasks even when other factors, such as age, intelligence, and working memory are factored out (Carlson & Moses, 2001). Inhibitory control and theory of mind share a similar developmental time-course, with advances in both arenas between the ages of 2 and 5.

One function that has been traced to the anterior cingulate is monitoring of error. One form of conflict was studied by having children play a Simple Simon game, which asked them to execute a response command given by one puppet while inhibiting commands given by a second puppet (Jones, Rothbart & Posner, in process). Children of 36-38 months showed no ability to inhibit their response and no slowing following an error, but at 39-41 months children showed both an ability to inhibit and slowing of reaction time following an error. These results suggest that between 30 and 39 months performance changes based upon detecting an error response. Because error detection has been studied using scalp electrical recording (Gehring, et al, 1992; Luu, Collins & Tucker, 2000) and shown to originate in the anterior cingulate (Bush, et al, 2000), we now have the means to examine the emergence of this cingulate function at around 2.5-3.5 years of age.

We have examined the ANT network tests in children of seven years of age using a version specifically adapted to them (see Figure 6). The results for children of this age are remarkably similar to those found for adults using the version of the task shown in Figure 2. The child reaction times are much longer but they show similar independence between the three networks. Children have much larger scores for alerting and conflict, suggesting that they have trouble in maintaining the alert state when not warned of the new target and in resolving conflict. This age (seven years) is amenable to neuroimaging using MRI. For example,

INSERT FIGURE 6 ABOUT HERE

children ages 5 to 16 years show a significant correlation between the volume of the area of the right anterior cingulate and the ability to perform tasks requiring focal attention (Casey, et al, 1997a). In a functional MRI study, performance of children ages 7-12 and adults were studied in a go/no-go task. In comparison with a control condition in which children responded to all stimuli, the condition requiring inhibitory control activated prefrontal cortex in both children and adults. Also, the number of false alarms in this condition correlated significantly with the extent of cingulate activity (Casey, et al, 1997b).

These studies provide evidence for the development of an executive network during early childhood. Moreover, the development of executive attention contributes to the socialization process by increasing the likelihood of learning important behaviors related to self-regulation and understanding the cognition and emotion of others. It seems likely that fostering the understanding of normal development of this system will illuminate pathologies of attention.

6. Cognitive Science Problems

Modularity

There has been a great deal of discussion in the cognitive psychology literature of the concept of modularity. These discussions have often defined modularity in a way which required a system to be unaffected by top down (attentional) influences. According to this

view only a very few vertical sensory and motor systems could be modular (Fodor, 1983). However, the evidence that even primary sensory systems can be modulated by attention makes it unlikely that any higher-level brain system will meet the criterion of modularity so defined.

Imaging data provides a rather different perspective on modularity. The material reviewed in this chapter suggests that even brain networks that reflect voluntary activity such as executive attention may be modular in the sense that very specific brain areas perform computations reflecting their component operations. This form of modularity does not suggest that these mechanisms will operate in the same way irrespective of strategy or context. However, they do provide a starting place for linking cellular and genetic mechanisms to brain areas and then to cognitive operations and behavior.

Early and Late Selection

One of the oldest issues in the field of attention is how early in processing can attention influence input. This issue arose before there was much discussion of specific brain mechanisms of attention. Many empirical studies were done to determine if attentional changes showed up as alterations in the beta (decision) parameter of a signal detection analysis or whether instead they involved changes in the d' (sensory) parameter (Hawkins, et al, 1990). Although many elegant studies were conducted attempting to clarify this issue, there has been no final resolution (although it seems likely that both parameters can be varied by some experimental conditions)(Hawkins, et al, 1990).

The early vs. late question can be resolved into three somewhat interdependent issues. 1) How early in the nervous system can attention influence stimulus input? The results suggest that it can be as early as V1 (Posner & Gilbert, 1999) under some conditions, but more often attention influences extrastriate visual areas (Kastner, et al, 1999). 2) How quickly after input can attention influence information processing? Again the cellular and physiological data indicate that it can be about as early as clear evidence of cortical processing can be obtained (Gilbert, in press), although in many situations the influence is not present until 80-100 msec after stimulus onset (Martinez, et al, 2001). The timing issue is of particular importance because activation of a particular brain area may be either along the input pathway, or could be due to feedback from higher areas. 3) What does early selection mean for the processing of information both selected and unselected? Here the answer is more complex. It seems to mean that certain aspects of complex scenes may be available for conscious report while other aspects will only be available if they succeed in producing reorienting. Unattended objects, however, may still be processed to fairly high levels and the processing itself may summon attention. The depth of cognitive processing of unattended objects and the possibility of attention to higher level codes suggests that early selection does not have the cognitive consequence originally implied. Selecting one stimulus over others does not mean that unselected items will not produce a reorienting of attention or still influence behavior (McCormick, 1997).

Priming

Priming refers to the influence of one event on the processing of subsequent events. Behavioral studies suggested that reaction time could be improved to a target by the presentation of a stimulus (prime) that shares a part of the same pathway. Priming can occur in either of two ways. In one way a stimulus activates a pathway automatically and a second stimulus that shares the same pathway is improved in performance (Posner, 1978). These effects can occur even when the prime is presented and masked so that subjects are not able to report its identity. A second way that priming can occur is if a person attends to some feature that will be shared by the target. For example, if people are taught that the word 'animal' should be interpreted as a body part, the target finger will be primed. The priming is from the subjects' attention to body part not from automatic activation of finger by the prime animal.

Data from imaging studies of priming by input and by attention support this distinction by showing very different effects on neural activity in the primed area. If priming occurs automatically by input the target shows reduced activation of the primed cells. On the other hand, attending to an area will enhance neural activity and increase the effect of the target (Corbetta, et al, 1991).

The newer imaging data shows the reality of the distinction between automatic priming and priming by attention. However, it is not at all clear how the brain brings about similar changes in performance sometimes by reducing and sometimes by increasing the activity of the target. This puzzle remains to be explained by future studies.

7. Relation to Neuropsychology

The ability to image the human brain has also provided new perspectives for neuropsychologists in their efforts to understand, diagnose and treat insults to the human brain that might occur as the result of stroke, tumor, traumatic injury, degenerative disease, or errors in development (Fernandez-Duque & Posner, 2000).

As we have argued, attention networks have anatomical and functional independence, but that they also interact in many practical situations. Damage to a node of these networks, irrespective of the source, produces distinctive neuropsychological deficits. This principle has been best established with respect to damage to the parietal lobe. Studies have shown that damage to parietal neurons that occur in stroke, due to degeneration in Alzheimers disease, blocking of cholinergic input, due to lesions of nucleus bassalis, temporary damage from transcranial magnetic stimulation, direct injections of scopolamine, or closed head injury all lead to difficulties in using cues to process targets in the visual field opposite the insult. Recently, normal persons who have one or two copies of the APOE4 gene which increases the risk of Alzheimer's Disease, have also been shown to have increased difficulty in orienting attention and in adjusting the spatial scale of attention, however, they had no difficulty with maintaining the alert state

(Greenwood, et al, 2000). Additional evidence for a common effect of damage to a node is reviewed in some detail elsewhere (Fernandez-Duque & Posner, 2001).

In one sense the convergence between imaging, lesions and pharmacology in terms of cognitive effect is obvious. If computations of parietal neurons lead to shifts of visual attention damage to these neurons should produce difficulties. Yet there has been the notion in neuropsychology that localization is not so important as the cause of the lesion. Moreover, there has also been the argument that imaging does not provide a good account of the computations that can predict the effect of damage (Uttal, 2001). Here we see that the imaging results provide clear evidence of the importance of areas of the parietal lobe in shifts of attention and damage to these areas regardless of cause interfering with orienting.

In addition, efforts to better understand the nature of brain disorder there have been efforts to adopt ideas related to the physical basis of attention for rehabilitation. Some recent studies have tried to rehabilitate specific attentional networks (Robertson, 1999; Sohlberg, McLaughlin, Pavese, Heidrich & Posner, 2000; Strum, Willmes, Orgass & Hartze, 1997). These studies suggest that rehabilitation procedures should focus on the particular attentional operations of the lesioned area, while at the same time considering the contribution of those deficits to other attentional functions.

In one study (Strum, et al, 1997), a computerized rehabilitation program was designed to try to enhance specific attentional networks. The authors concluded from these findings that vigilance and alertness are the most fundamental functions in the hierarchy, and that selective attention and divided attention recruit these functions for their normal operation. Another study that utilized a practice-oriented therapy (attention process therapy) with brain-injured patients showed an overall improvement in performance (Sohlberg, et al, 2000). In some tasks the group that had relatively high vigilance scores showed better effects of the therapy in agreement with the Strum idea.

A third rehabilitation study tested the possible interaction between vigilance and orienting by training patients to increase their self-alertness, and exploring whether the rehabilitation of self-alertness had an impact on patients' neglect (i.e., orienting deficit) (Robertson, Tegnér, Tham, Lo & Nimmo-Smith, 1995). Exogenous alertness was used as a basis for training patients to self-alert. External warning signals were presented, and patients were instructed to generate a self-alertness signal in response to it. Exogenous alertness, as produced by a loud noise, depends on a thalamo-mesencephalic path and is relatively unimpaired in right parietal patients. After the training procedure was explained, the patient started the task and at variable intervals the experimenter knocked on the table while at the same time saying "Attend!" in a loud voice. At the next stage in the training, it was the patient who shouted "Attend!" each time the experimenter knocked on the table. Later, the patient would do both the knocking and the vocal command, first loudly, then subvocally, and finally mentally. Patients were encouraged to try this self-alertness method in their everyday life. This rehabilitation training not only improved patients' self-alertness, but also reduced the extent of their spatial neglect.

The availability of imaging as a means of examining brain networks prior to and following rehabilitation should provide new opportunities for research that could fine-tune both behavioral and pharmacological intervention methods. Genetic analysis could also aid in an understanding of who might benefit from particular forms of therapy. Taken together these methods and the analysis of attention networks described in this and subsequent papers in this section could provide significant new approaches to rehabilitation following brain injury

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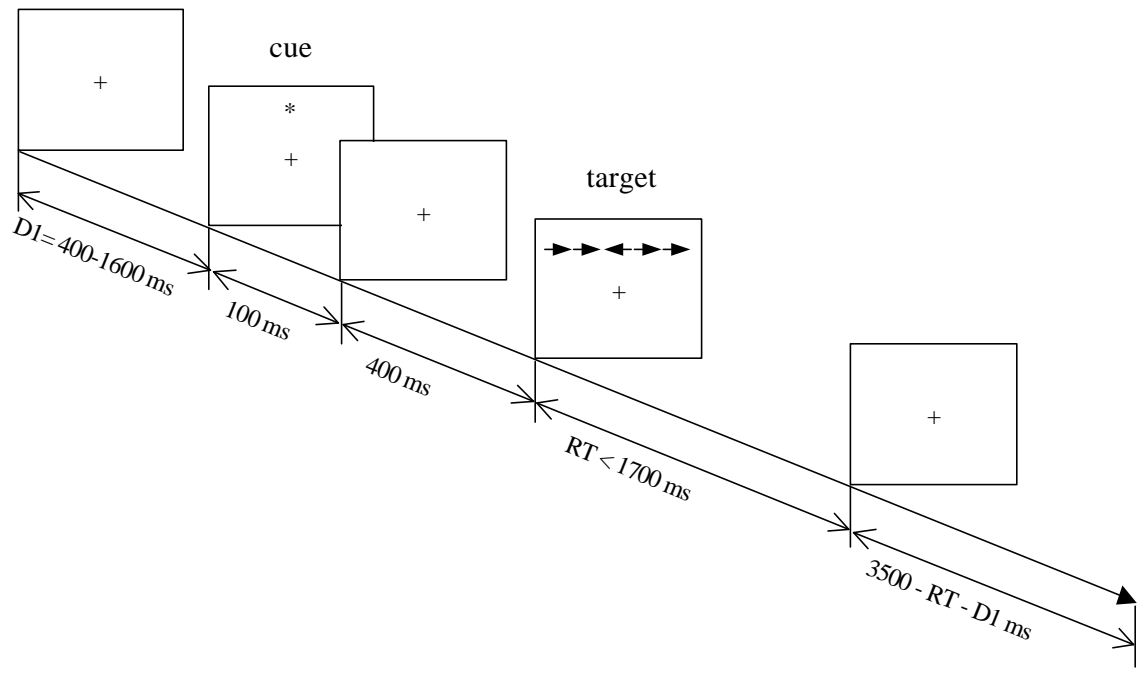
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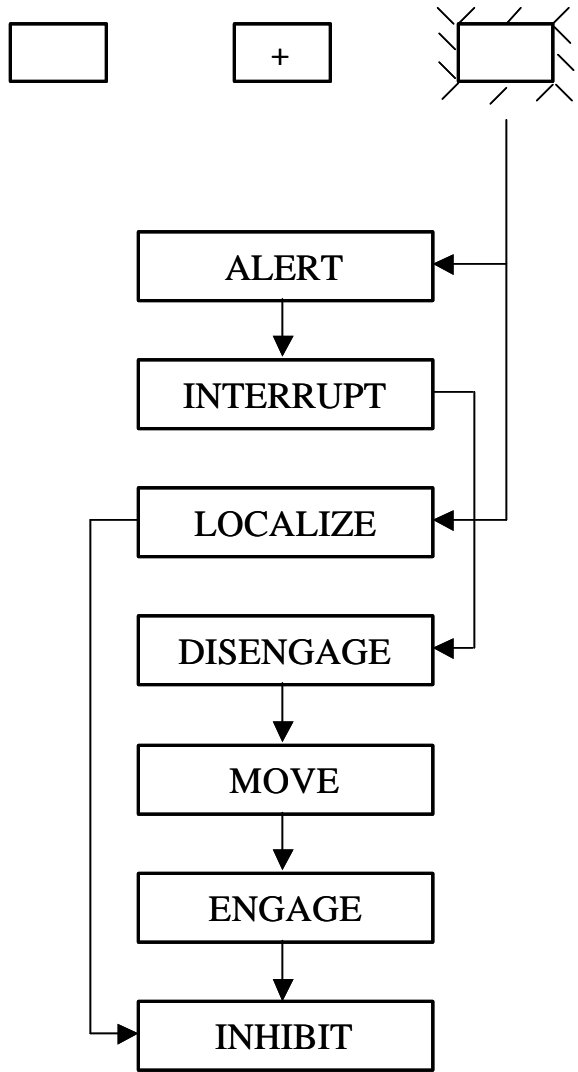
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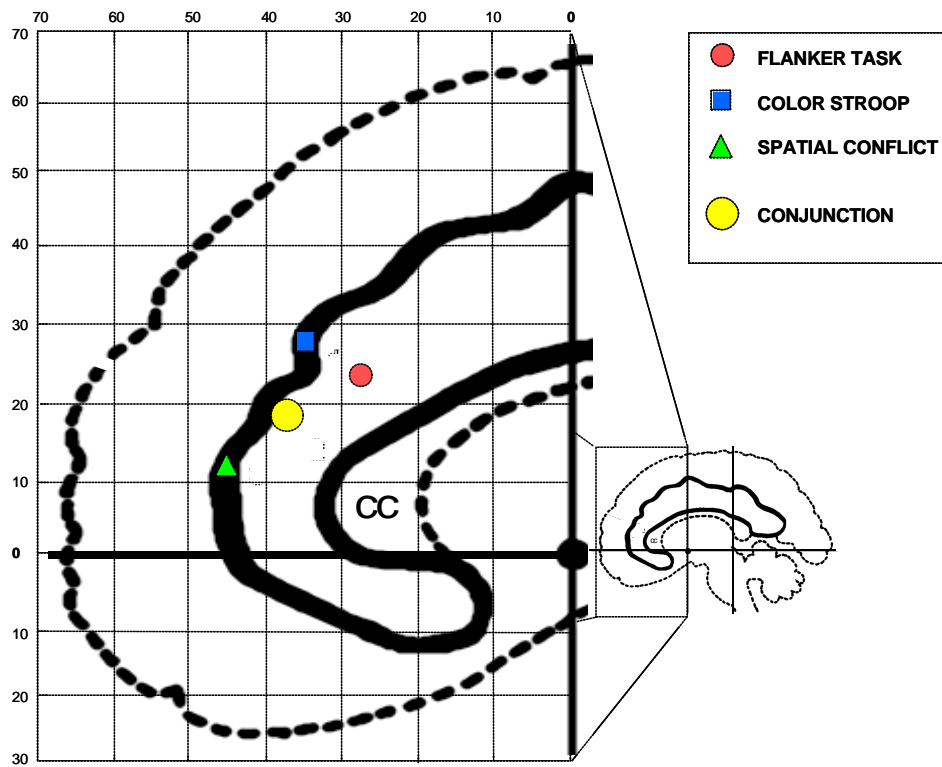
Figure Captions

- Figure 1 Brain structures that are networks found active in studies of the three functions of attention, dominant neuromodulators and the sites where that function has its influence.
- Figure 2 The Attention Network Test. The cue provides information of when and where the target will occur. The target is a central arrow that indicates a left or right response surrounded by congruent or incongruent flankers.
- Figure 3 A view of orienting of attention proposed in the 1980s. In this view the superior parietal lobe was involved in the operation of disengaging attention, the colliculus in moving it and the pulvinar in engaging the target (Posner, 1988). More recent view discussed in this chapter indicate that the superior parietal areas seem related to voluntary movements of attention, while disengaging to handle novel inputs appears to involve the temporal parietal junction.
- Figure 4 View of the anterior cingulate. Small dot indicates color Stroop task, triangle indicates spatial conflict task, square indicates flanker task and large circle indicates the conjunction of the three conflict tasks.
- Figure 5 Subtraction used to obtain values for the three networks. Average refers to the mean value for forty normal persons. Heritability refers to the results of a twin study described in the text.
- Figure 6 Upper panel shows the stimuli used for seven year old children in the ANT. Bottom panel compares adults and children R.T. both using this version of the ANT.

FUNCTION	STRUCTURES	MODULATOR	SITES
Orient	Superior Parietal	Acetylcholine	V1, A1,S1
	Temporal parietal Junction		
	Frontal eye fields		
	Superior Colliculus		
Alert	Locus Coruleus	Nor epinephrine	Orient System
	Right frontal and		
	parietal cortex		
Exec. Attn.	Ant. Cingulate	Dopamine	All brain areas
	Lateral ventral		
	Prefrontal		
	Basal Ganglia		







Network	Measurement	Average Value*	Heritability**
Executive	$RT_{\text{Incongruent}} - RT_{\text{Congruent}}$	84	.89
Alerting	$RT_{\text{Double cue}} - RT_{\text{No cue}}$	47	.18
Orienting	$RT_{\text{Valid cue}} - RT_{\text{Central cue}}$	51	0

* As measured from 40 normal subjects (Fan et al, in press)

** From a study of 26 pairs of monozygotic and 26 pairs of same sex dizygotic twins (Fan et al, 2001b)

