BRAIN MECHANISMS AND LEARNING OF HIGH LEVEL SKILLS

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ABSTRACT

Progress in neuroimaging and in sequencing the human genome make it possible to think about high level cognitive skills in terms of experiential and genetic factors that shape development of underlying neural networks. We have carried out an extensive series of investigations of an executive attention network related to self-regulation of cognition and emotion. This network involves a specific anatomy that includes midline and lateral frontal areas. We have used a number of conflict tasks shown to activate these brain areas to study the development of the network during early childhood. Individual differences in the development of this network have been related to parental reports of the ability of children to regulate their behavior, to delay reward and to develop an understanding of the minds of others. We have found two genes that show a relationship to individual efficiency in resolving conflict. As predicted, these genes were also related to the degree of activation of the anterior cingulated, which is a node of this network. We found alleles of two genes that are related to individual efficiency in performance and the degree of activation of a node of this network in the anterior cingulate gyrus. We are examining whether specific training experiences can influence the development of this network in four-year-old children. These studies open the way to investigating the role of genes and experience in preparing preschool children for acquiring skills during their early school years.

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INTRODUCTION

Two major developments have greatly altered the prospects for making a connection between common networks of the human brain and theories of how people differ. First, with the development of neuroimaging, we could glimpse inside the human brain as people think (Posner & Raichle, 1994). When combined with electrical or magnetic recording from outside the skull, it was possible to see in real time the circuits involved in computing aspects of a task. Although some parts of this technology had been around for a long time, only in the past fifteen years did it become clear that we could create local images of the functioning anatomy of the human brain.

At the beginning of the 20^{th} century, Santiago Ramon y Cajal (1937) was able for the first time to observe individual nerve cells. Our current ability to see into the human brain depends on the operation of these nerve cells. When neurons are active, they change their own local blood supply. This makes it possible to trace areas of the brain that are active during cognitive processes by measuring local changes in aspects of the brain blood supply.

The second major development at the end of the 20^{th} century was the sequencing of the entire human genome (Ventner, Adams, Myers, Li, et al, 2001). Now it was possible not only to study the functional anatomy of brain networks, but also to examine how genetic differences might lead to individual variation in the potential to use these networks in the acquisition and performance of skills. However, the route from genetic endowment to performance would be neither simple nor separate from an understanding of the brain networks themselves. Taken together, these developments open up the opportunity to examine the networks that underlie the self-regulation of thoughts, emotions and behavior needed to succeed in school.

ATTENTION NETWORKS

Functional neuroimaging has allowed many cognitive tasks to be analyzed in terms of the brain areas they activate, and studies of attention have been among the most often examined in this way (Corbetta & Shulman, 2002; Driver, Eimer & Macaluso, in press; Posner & Fan, in press). Imaging data have supported the presence of three networks related to different aspects of attention. These networks carry out the functions of alerting, orienting and executive control (Posner & Fan, in press). A summary of the anatomy and transmitters involved in the three networks is shown in Table 1.

INSERT TABLE 1 ABOUT HERE

Alerting is defined as achieving and maintaining a state of high sensitivity to incoming stimuli; orienting is the selection of information from sensory input; and executive control involves the mechanisms for monitoring and resolving conflict among thoughts, feelings and responses. The alerting system has been associated with thalamic as well as frontal and parietal regions of the cortex (Fan et al, in press). A particularly effective way to vary alertness has been to use warning signals prior to targets. The influence of warning signals on the level of alertness is thought to be due to modulation of neural activity by the neurotransmitter norepinepherine (Marrocco & Davidson, 1998).

Orienting involves aligning attention with a source of sensory signals. This may be overt, as when eye movements accompany movements of attention, or may occur covertly without any eye movement. The orienting system for visual events has been associated with posterior brain areas including the superior parietal lobe and temporal parietal junction and in addition, the frontal eye fields (Corbetta & Shulman, 2002). Orienting can be manipulated by presenting a cue indicating where in space a target is likely to occur, thereby directing attention to the cued location (Posner, 1980). Event related functional magnetic resonance imaging (fMRI) studies have suggested that the superior parietal lobe is associated with orienting following the presentation of a cue (Corbetta & Shulman, 2002). The superior parietal lobe in humans is closely related to the lateral intraparietal area (LIP) in monkeys, which is known to produce eye movements (Andersen, 1989). When a target occurs at an uncued location, and attention has to be disengaged and moved to a new location, there is activity in the temporal parietal junction (Corbetta & Shulman, 2002). Lesions of the parietal lobe and superior temporal lobe have been consistently related to difficulties in orienting (Karnath, Ferber & Himmelbach, 2001).

Executive control of attention is often studied by tasks that involve conflict, such as various versions of the Stroop task. In the Stroop task, subjects must respond to the color of ink (e.g. red) while ignoring the color word name (e.g. blue) (Bush, Luu & Posner, 2000). Resolving conflict in the Stroop task activates midline frontal areas (anterior cingulate) and lateral prefrontal cortex (Botvinick, Braver, Barch, Carter & Cohen, 2001; Fan, Flombaum, McCandliss, Thomas & Posner, 2003). There is also evidence for the activation of this network in tasks involving conflict between a central target and surrounding flankers that may be congruent or incongruent with the target (Botvinick, et al., 2001; Fan, et al, 2003). Experimental tasks may also provide a means of fractionating the functional contributions of different areas within the executive attention network (McDonald, Cohen, Stenger & Carter, 2000). Recent neuroimaging studies have provided evidence that the executive attention network is involved in self-regulation of positive and negative affect (Beauregard, Levesque, & Bourgouin, 2001; Ochsner Kosslyn, Cosgrove, Cassem, et al, 2001) as well as in a wide variety of cognitive tasks that underlie intelligence (Duncan, Seitz, Kolodny, Bor, et al, 2000).

INDIVIDUALITY

Almost all studies of attention have been concerned with either general abilities 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 (ANT, see Figure 1) that examines the efficiency of the three brain networks we have described above (Fan, McCandliss, Sommer, Raz & Posner, 2002).

INSERT FIGURE 1 ABOUT HERE

The data provide three numbers representing the skill of each individual in the alerting, orienting and executive networks. In a sample of 40 normal persons, we found each of these indexes to be reliable over repeated testing; in addition, no correlation was found.

The ability to measure individual differences in attention among adults raises the question of the degree to which attention is heritable. To address 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, 2001). We found strong correlations between the monozygotic twins for the executive network measure. This led to an estimate of heritability of the executive network of 0.89. Because of the small sample, the estimate of 95 percent confidence interval for heritability is between 0.3 and 0.9. Nonetheless, these data support a role for genes in the efficacy with which the executive network is put into action.

As a way of searching for candidate genes that might relate to the efficiency of these networks, we used the association of the executive network with the neuromodulator DA (Fossella, Sommer, Fan, Wu, et al, 2002). To do this, we ran 200 persons in the ANT and genotyped them to examine frequent polymorphisms in genes related to their respective neuromodulators. We found significant association of two genes related to dopamine, the DRD4 and MAOA genes. We then conducted a neuroimaging experiment in which we compared persons with two different alleles of these two genes while they performed the ANT. We found that these alleles produced different activation within the anterior cingulate, which is a major node of this network (Fan, et al, 2003).

EARLY CHILDHOOD

Development of the network involved in orienting to visual objects has been traced to early infancy (Haith, Hazan & Goodman, 1988; Clohessy, Posner & Rothbart, 2001). However, infants perform poorlywith ambiguity that introduces conflict between responses (Clohessy, Posner & Rothbart, 2001). The ability to resolve conflict is an important part of the executive attention network and this does not seem to be available until about 2 years of age.

Developmental changes in the control of cognition by 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 (the 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 (Fan, et al., 2002). Children 24 months of age tended to fix on a single response, while 36-month-old children performed at high accuracy levels, but like adults responded more slowly and with reduced accuracy to incompatible trials.

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, Ahadi & Hershey, 1994), to be inversely related to temperamental 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 (Rothbart, et al, 1994). 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.

These studies suggest two routes to successful socialization. A strongly reactive amygdala in more fearful children 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 the signals 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, Murray, Jacques, Koenig & Vandegeest, 1996). Two separable control systems, one reactive (fear) and one self-regulative (effortful control) appear to regulate the development of conscience. In support of the link between effortful control and social behavior, Ellis (2002) found that, for adolescents, effortful control and poor ability to control conflict as measured by the ANT, separately predicted antisocial behavior.

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 are correlated 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 areas between the ages of 2 and 5.

PRESCHOOL

We have traced the development of executive attention into the preschool period (Rueda, Fan, McCandliss, Halparin, Gruber, Pappert & Posner, in press) by using a version of the ANT adapted for children (see Table 2). In some respects, results are remarkably similar to those found for adults using the version of the task shown in Figure 1. The reaction times for the children 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. Rather surprisingly, as measured by the ANT, the ability to resolve conflict in the flanker task remains about the same from age seven to adulthood (see Table 2).

INSERT TABLE 2 ABOUT HERE

There is considerable evidence that the executive attention network is of great importance in the acquisition of school subjects such as literacy (McCandliss, et al 2002) and in a wide variety of other subjects that draw upon general intelligence (Duncan, et al, 2000). It has been widely believed by psychologists that training always involve specific domains, and that more general training of the mind, for example, by formal disciplines like mathematics or Latin, did not generalize outside of the specific domain trained (Thorndike, 1899; Simon, 1969). However, attention may be an exception. It is both a domain that involves specific brain mechanisms, as we have seen, but whose function is to influence the operation of other brain networks (Posner & Fan, in press; Posner & Petersen, 1990). Moreover, anatomically the network involving resolution of conflict overlaps brain areas related to general intelligence (Duncan, et al, 2002). Training of attention either explicitly or implicitly is also often a part of the school curriculum (Mills & Mill, 2000) but little research is available to determine exactly how and when attention training can best be done.

A central aspect of the executive attention network is the ability to deal with conflict. We used this feature to design a set of training exercises that were adapted from efforts to send macaque monkeys into outer space (Rumbaugh & Washburn, 1995). These exercises resulted in monkeys' ability to resolve conflict in a Stroop-like task (Washburn, 1994).

Our exercises began with training the child to control the movement of a cat by using a joystick as well as prediction of where an object would move, given its initial trajectory (see Figure 2). Other exercises emphasized the use of working memory to retain information for a matching to sample task and the resolution of conflict (see Figure 3).

INSERT FIGURES 2 AND 3 ABOUT HERE

We have tested the efficacy of a very brief five days of attention training with groups of 4-year-old children. The children were brought to the laboratory for seven days for sessions lasting about 40 minutes. These sessions were conducted over a two to three week period. The first and last days were used to assess the effects of the training by use of the ANT, a general test of intelligence (the K-BIT, Kaufman & Kaufman, 1990 and a temperament scale (the Children Behavior Questionnaire or CBQ). During the administration of the ANT, we recorded 128 channels of EEG in order to observe the amplitude and time course of activation of the anterior cingulate (Rueda, Fan & Posner, 2003).

During our first experiment, we compared twelve children who underwent our training procedure with twelve who were randomly selected and took no training, but came in twice for assessment. In our second experiment we again used 4-year-olds, but the control group came in seven times and saw videos which required an occasional response on their part to keep them playing. All of the children seemed to enjoy the experience (see Figure 4) and their caregivers were quite supportive of the effort.

INSERT FIGURE 4 ABOUT HERE

In this paper we illustrate the training exercises in Figures 2-4 and present a brief overview of our initial results. Of course, five days is a minimal amount of training to influence the development of networks that develop for many years. Nonetheless, we found a general improvement in intelligence in the experimental group as measured by the K-BIT. This is due to improvement of the experimental group in the non-verbal portion of the IQ test. We also discovered that the RT measures registered with the ANT were highly unstable and of low reliability in children of the age we were testing; thus we were not able to obtain significant improvement in the measures of the various networks, although overall reaction time did improve. We did not observe changes in temperament over the course of the training. Our preliminary analysis of the brain networks using EEG recording suggested that the component most closely related to the anterior cingulate in prior studies could be seen in the four-year-olds, and the component became apparent at a lower latency in the trained children, but this conclusion will require further analysis. Because of the variability of RT in the four-year-old children, we are currently replicating our study with six-year-olds. We are also studying the early acquisition of word knowledge, using a program called word building (McCandliss, et al, 2002) in samples of children who have previously undergone attention training and control children. These studies remain to be completed.

As the number of children who undergo our training increases, we can examine aspects of their temperament and genotype to help us understand who might benefit from attention training. To this end we are currently genotyping all of the children in an effort to examine the candidate genes found previously to be related to the efficacy of the executive attention networks. We are also beginning to examine the precursors of executive attention in even younger children, with the goal of determining whether there is a sensitive period during which interventions might prove most effective.

There is already some evidence in the literature with older children who suffer from attention deficit hyperactivity disorder (ADHD) that using attention training methods can produce improvement in the ability to concentrate and in general intelligence (Kerns, Esso & Thompson, 2000; Klingberg, Forssberg & Westerberg, 2002; Shavlev, Tsal & Mevorach 2002). As a result, we are also working with other groups to carry out these exercises in children with learning related problems such as ADHD and autism. These projects will test whether the programs are efficacious with children who have special difficulties with attention as part of their disorder. We hope also to have some preschools adopt attention training as a specific part of their preschool curriculum. This would allow training over more extensive time periods, and testing of other forms of training such as could occur in social groups (Mills & Mills, 2000).

While we do not yet know whether our specific program is effective, much less optimal, we believe that the evidence we have obtained for the development of specific brain networks during early childhood provides a strong rationale for sustained efforts to see if we can improve the attentional abilities of children. In addition, it would be possible to determine how well such methods might generalize to the learning of the wide variety of skills that must be acquired during school.

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Figure Captions

Figure 1: Schematic of the Attention Network Test (ANT) developed by Fan, et al (2002) to study individual differences in the three attentional networks. a) illustrates the four cue conditions; b) the three types of target; c) the sequence of events; and d) the subtractions to indicate the efficiency of each network.

Figure 2: Tracking exercises. a) The child's task is to move the cat under a moving umbrella to avoid the rain, once the umbrella is caught, the child has to keep the cat under it as the umbrella continues moving around; b) The child moves the cat to the grass to avoid the mud. Over trials, the amount of grass is reduced and the mud increased until considerable concentration is required of the child to move the cat to a grassy section, c) The child moves the cat to intercept the duck as it exits the pond. As the duck always swims in a straight line, in this exercise, the child will learn to predict where it will come out of the pond.

Figure 3: Visual attention and conflict resolution exercises. a) Matching-to-sample exercise. The child must select the picture on the brown board that matches the sample on the upper left corner. Matching to sample difficulty is increased over the trials by making the competing pictures more similar. At advanced levels, the sample picture is removed from the screen and the child has to memorize it in order to select the correct matching picture; b) Conflict resolution exercise. The child has to select the group with the most numbers on it. In congruent trials, like the one illustrated, the more numerous group is made up of numbers larger in value. In incongruent trials, the more numerous group is made up of numbers smaller in value. c) Illustration of the visual feedback for completing a set of trials of equal difficulty.

Figure 4: Illustrates the high level of concentration of a four year old child during attention training.

Table 1. Anatomical structures and neuromodulators related to each of the three attentional networks.

FUNCTION	STRUCTURES	MODULATOR
Orient	Superior parietal Temporal parietal junction Frontal eye fields Superior colliculus	Acetylcholine
Alert	Locus Coeruleus Right frontal and parietal cortex	Norepinephrine
Executive attention	Anterior cingulate Lateral ventral prefrontal Basal ganglia	Dopamine

Table 2. *Development of efficiency of the attentional networks. Study 1 shows development from 6 to 10 years of age as measured by the child version of the ANT. Study 2 compares 10 year old children with adults using both the adult and child versions of the ANT.*

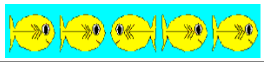
Child ANT							
		Attentional Networks Subtractions					
Study	**Age**	**Alerting**	**Orienting**	**Conflict**	**Conflict for errors**	**Overall RT**	**Overall error rates**
1	6	79 (75)	58 (76)	115 (80)	15.6	931 (42)	15.8
	7	100 (75)	62 (67)	63 (83)	0.7	833 (125)	5.7
	8	73 (67)	63 (66)	71 (77)	-0.3	806 (102)	4.9
	9	79 (47)	42 (48)	67 (38)	1.6	734 (68)	2.7
2	10	41 (47)	46 (44)	69 (44)	2.1	640 (71)	2.2
	adults	30 (32)	32 (30)	61 (26)	1.6	483 (36)	1.2
Adult ANT		← ← → ← ←					
2	10	78 (61)	60 (56)	156 (76)	3.9	710 (90)	2.8
	adults	40 (34)	52 (35)	131 (62)	4.7	532 (54)	2

Figure 1

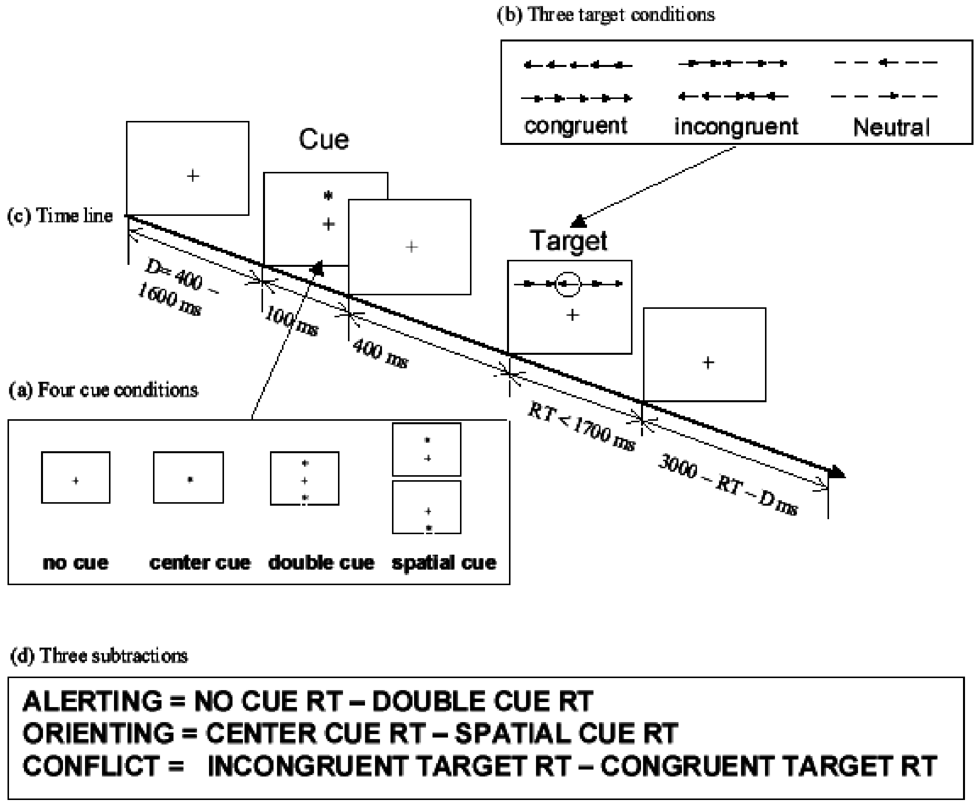

(b) Three target conditions
congruent
incongruent
Neutral
Cue
Target
(c) Time line
D= 400 – 1600 ms
100 ms
400 ms
RT < 1700 ms
3000 – RT – D ms
(a) Four cue conditions
no cue
center cue
double cue
spatial cue
(d) Three subtractions
ALERTING = NO CUE RT – DOUBLE CUE RT
ORIENTING = CENTER CUE RT – SPATIAL CUE RT
CONFLICT = INCONGRUENT TARGET RT – CONGRUENT TARGET RT

Figure 2

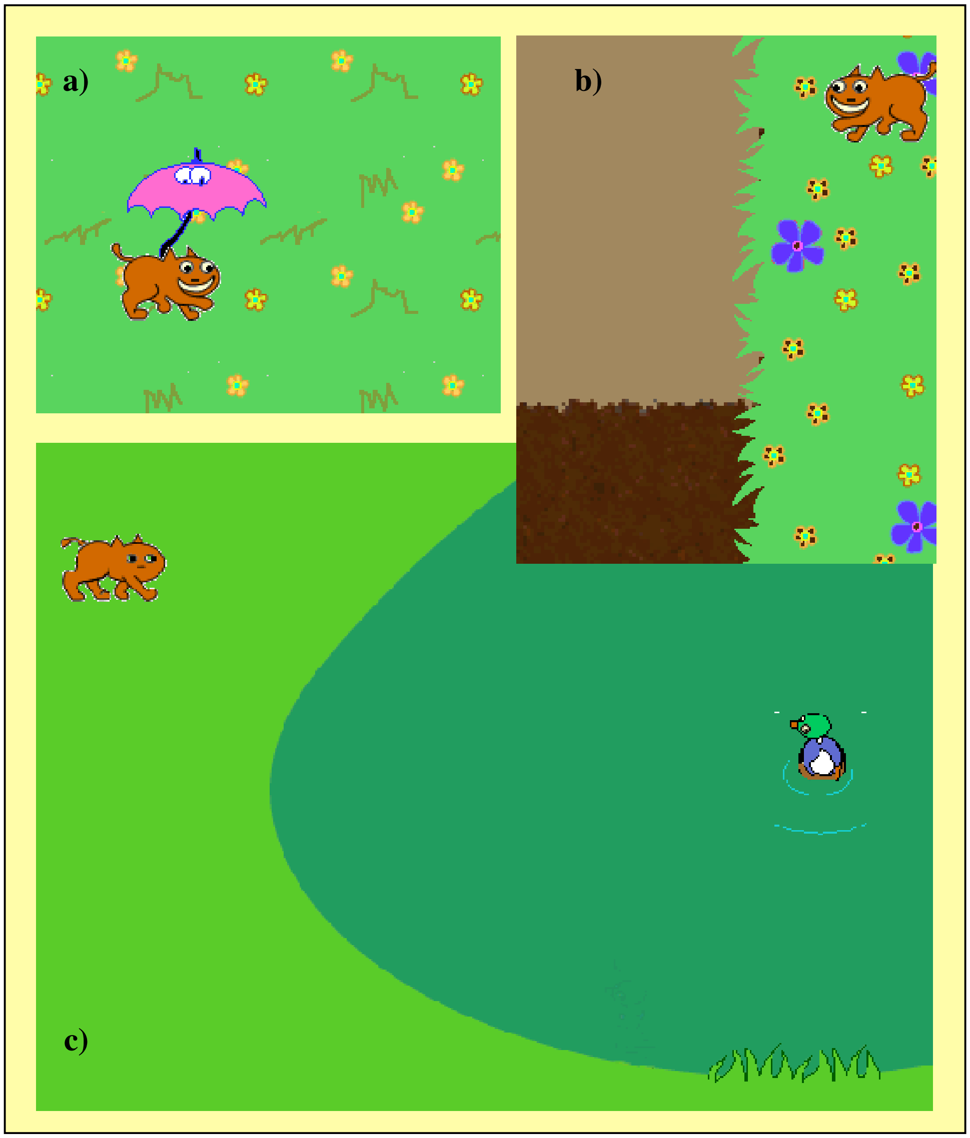


Figure 3

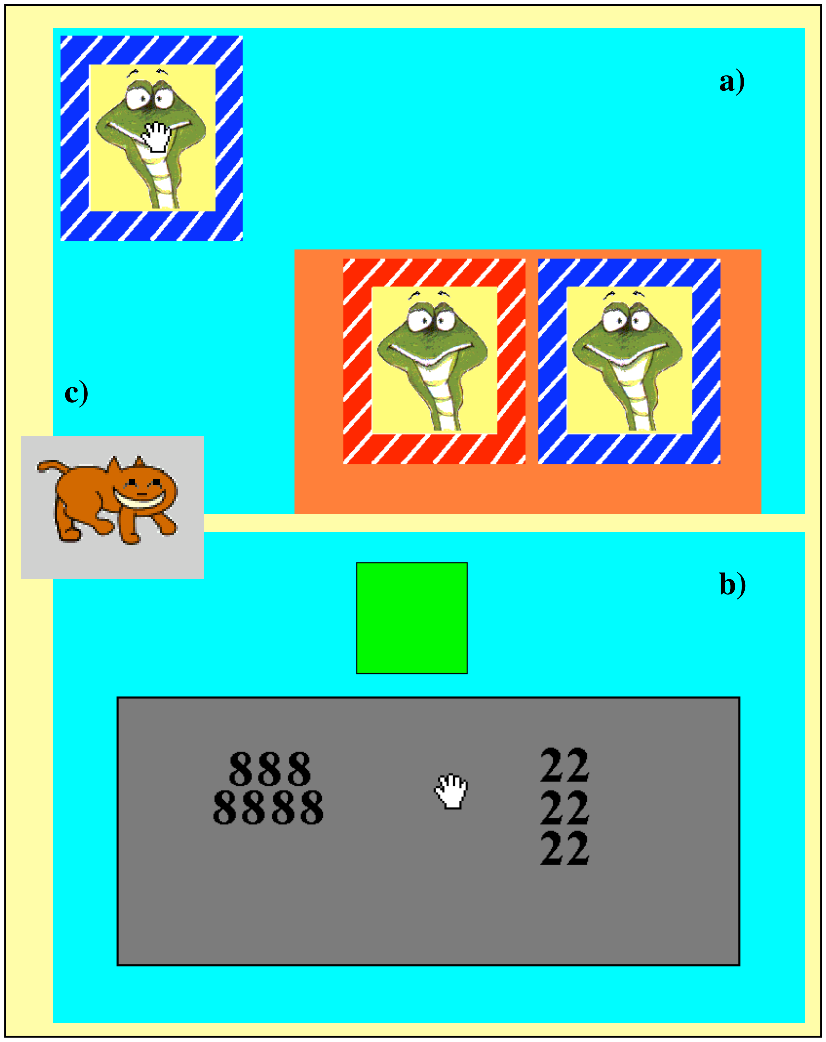


Figure 4