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PERSPECTIVES

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Restoring Attention Networks

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The attention networks of the human brain have been under intensive study for more than twenty years and deficits of attention accompany many neurological and psychiatric conditions. There is more dispute about the centrality of attention deficits to these conditions. It appears to be time to study whether reducing deficits of attention alleviate the neurological or psychiatric disorder as a whole. In this paper we review human and animal research indicating the possibility of improving the function of brain networks underlying attention and their potential clinical role.

INTRODUCTION

Neuroimaging has allowed researchers to determine with increasing precision the brain areas involved in many human activities. Prominent among these has been the study of brain networks of attention. In this paper we describe the potential utility of this knowledge for the diagnosis and treatment of common neurological and psychiatric illnesses involving attention.

In our previous work we have identified three different brain networks related to the functions of attention [1]. These are:

(i) Obtaining and maintaining the alert state, involving the brain's norepinephrine system including the locus coeruleus in the pons and frontal and parietal cortical areas.

(ii) Orienting to sensory stimuli, involving both ventral and dorsal frontal and parietal areas and subcortical areas of the superior colliculus and pulvinar.

(iii) The executive attention network that controls voluntary responses (Executive attention) involving the anterior cingulate, anterior insula, and underlying striatum. (See Table 1;[2].)

These networks play a strong role in the regulation of behavior, both in the control of positive and negative affect and of the sensory input, and also give rise to consciousness of content and voluntary behavior. Imaging brain networks of attention have allowed us to identify the dominant neuromodulator of each network and to study genes related to these modulators. (See Table 1;[3].)

By use of the Attention Network Test (ANT†) (see Figure 1) scores for each of these attention networks can be obtained individually from children and adults [4].

ANT scores have also been used to compare patients suffering from various conditions with normal groups. Abnormal scores for each network of attention have been associated with mental disorders. We summarize these associations below and in Table 2.

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†Abbreviations: ANT, Attention Network Test; ADHD, Attention-deficit/hyperactivity disorder; OCD, Obsessive-Compulsive Disorder; ACC, anterior cingulate cortex.

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Table 1*. Brain areas and Neuromodulators Involved in Attention Networks.

NETWORKS	STRUCTURES	MODULATOR
Orienting	Superior parietal Temporal parietal junction Frontal eye fields Superior colliculus Pulvinar	Acetylcholine
Alerting	Locus Coeruleus Frontal and parietal cortex	Norepinephrine
Executive	Anterior cingulate Anterior Insula Basal ganglia	Dopamine

*Adapted from Posner, MI. Attention in the Social World. Oxford: Oxford University Press; 2012.

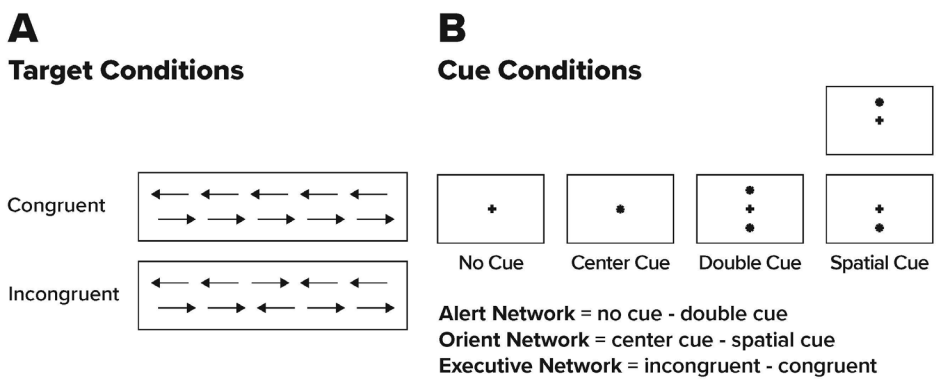

Figure 1. The Attention Network Test uses a target surrounded by flankers see A for target types. Before the target appears cues are given see (B) for cue types. Reaction time is the dependent measure and bottom panel shows the scores for the alerting, orienting and executive (conflict) network (adapted from Fan *et al* 2002 [4]).

ATTENTIONAL PATHOLOGIES

Attentional difficulties are frequently associated with brain injury and with many psychopathologies. Without an understanding of the neural substrates of attention, systematic efforts to remedy these attentional problems have been difficult. This situation may change with the application of our understanding of attentional networks to pathological issues. In the volume *Attention in a Social World*, [5], many forms of pathology briefly summarized in Table 2 are discussed in greater detail. Table 2 and the references cited there provide details on the central importance of attention to each of the pathologies. We do not think a one to one correspondence between network, disorder, and symptom is a complete story. Many disorders involve more than one network and often the networks change in the development of the disorder. For example, Attention-deficit/hyperactivity disorder (ADHD) appears to involve alerting early on and later a deficit in executive attention. Moreover, disorders have multiple symptoms. In Table 2 we use the most prominent connections between network and disorder and describe a typical symptom of the disorder.

In this paper, we attempt to tie the brain networks revealed by imaging studies to underlying cells and their connections found in various animal models. We have recently reviewed evidence for the role of attention in obsessive compulsive disorder [6]. Repetitive concentration of attention upon a potential failure appears a key feature of this disorder. Animal models have suggested that abnormal loops between anterior cingulate and striatum may be involved in Obsessive-Compulsive Disorder (OCD) [7]. The reactivation of this circuit may underlie the problem of repetitive attention to negative events.

Similar findings occur in a variety of other anxiety disorders [8]. Anxiety disorders often involve unreasonable fear (see Table 2). In an effort to link brain networks to underlying cellular mechanisms, a mouse study has found that stimulation of a circuit from the amygdala to the striatum either by laser stimulation or by inducing a reward can improve extinction of fear [9]. In addition, anxiety disorders have been identified with reduced

Table 2. Disorders Associated With Attention Networks.

Attention Network	Condition	Symptoms
Alerting	Aging	Sleep disorder (a)
	ADHD	Sleep disorder, hyperactivity, concentration (b,c)
Orienting	Autism	Disengage deficit (d,e)
	PTSD	Difficulty in disengaging from fearful stimuli (f)
	Neglect	Reorienting in contralesional direction (g)
Executive	Anxiety Disorders	Difficulty inhibiting fear (h)
	Depression	Dwell on negative ideation (i)
	OCD	Recurring thoughts, images or behaviors (j)
	Personality Disorder Borderline	Negative ideation, lack of control (k)
	Schizophrenia	Hallucinations (l)
	Substance Abuse	Compelled behavior (m)

(a). Fernandez-Duque D, Black SE. Attentional networks in normal aging and Alzheimer's disease. Neuropsychology. 2006;20:133–43. (b). Halperin JM, Schulz KP. Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. Psychol Bull. 2006;132:560–81. (c). Johnson KA, Robertson IH, Barry E, et al. Impaired conflict resolution and alerting in children with ADHD: evidence from the ANT. J Child Psychol Psychiatry. 2008;49:1339–47. (d). Landry R, Bryson SE. Impaired disengagement of attention in young children with autism. J Child Psychol Psychiatry. 2004;45:1115–22. (e). Towsend J, Courchesne E. Parietal damage and the narrow spotlight of spatial attention. J Cogn Neurosci. 1994;6:220–32. (f). Levy BJ. Controlling intrusive memories. Unpublished doctoral dissertation University of Oregon, 2008. (g). Posner MI, Walker JA, Friedrich FJ, Rafal RD. J Neurosci. 1984;4(7):1863-1874. (h). Ghassemzadeh H, Rothbart MK, Posner MI. Anxiety and Brain Networks of Attentional Control. Journal of Cognitive and Behavioral Neurology. Forthcoming. (i). Drysdale AT, Grosenick L, Downar J, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2016;23(1):28-38. (j). Ghassemzadeh, Habibollah. Mechanisms of Response Prevention and the Use of Exposure as Therapy for Obsessive-Compulsive Disorder. International Journal of Psychiatry. 2017;2(1). (k). Posner MI, Rothbart MK, Vizueta N, et al. Attentional mechanisms of borderline personality disorder. Proc Natl Acad Sci U S A. 2002;99(25):16366-70. (l). Wang KJ, Fan J, Dong Y, Wang C, Lee TM, Posner MI. Selective impairment of attentional networks of orienting and executive control in schizophrenia. Schizophr Res. 2005;78(2-3):235-41. (m). Tang YY, Tang R, Posner MI. Brief meditation training induces smoking reduction. Proc Natl Acad Sci U S A. 2013;110(34):13971–5.

thickness of the anterior cingulate and insula cortex in early life [10]. The anterior cingulate cortex (ACC) and insula are key nodes in the executive attention network which undergo extensive development in childhood [11]. Similar efforts link the executive attention network to underlying cells, neuromodulators, and genes [3].

STIMULATING THE BRAIN

Understanding attentional networks may set the stage for possible treatments of disorders involving deficits in brain connectivity related to attention. We have been carrying out studies designed to test whether such treatment is possible. Our work began with studies of meditation training [12], we found that one month of meditation training altered the white matter connections in areas surrounding the anterior cingulate. We speculated that the alteration of white matter was due to the strong theta (4 to 8 Hz) rhythm found over the frontal midline following training [13].

To test this idea, mice were bred so that neuronal output of the anterior cingulate could be excited or inhibited with laser light (optogenetics) [14,15] We implanted lasers in the anterior cingulate of the mice and found that for mice stimulated with low frequency rhythms so that the output neurons of the anterior cingulate showed a rhythmic increase in spikes, there was an increase in oligodendrocytes (cells that create myelin) and a decrease in the ratio of axon diameter to axon diameter + myelin (g ratio). Mice who had low frequency stimulation showed less fear and more exploration than did un-stimulated controls. This was demonstrated in a box that contained dark and light compartments. The stimulated mice spent more time in the light than controls. These findings show that connectivity can be improved by low frequency rhythms such as those produced by meditation training. Moreover changing the properties of white matter pathways surrounding the anterior cingulate reduced fear and improved exploration [15].

The optogenetic method requires procedures that are too invasive to allow testing in humans. We sought to determine if there is a method for non- or minimally invasive stimulation to increase intrinsic theta range oscillations in the ACC [16]. We used sensory (auditory) input, neurofeedback, and electrical stimulation presented with and without a task that also stimulated the ACC. In the electrical condition we used alternating current at 6 Hz and 100 milliamps delivered by a set of 10 elec-

trodes over the frontal midline. One minute of auditory or electrical stimulation was alternated with a minute of no stimulation. Only the minute with no external stimulation was used to assess the effects of the input on intrinsic theta levels.

Comparing the three methods [16], electrical stimulation while performing the Attention Network Test [4] was the most effective in produced significant increases in theta during a minute of non-stimulation following a minute of electrical stimulation. The 6 Hz auditory stimulation also appeared to increase theta, but this was not significant statistically.

In this study all participants used the same generic set of electrode locations previously, shown by simulation to activate the ACC [17]. A new study compared these generic electrode locations with individual ones chosen using the anatomy from structural MRI to construct a different head model for each participant [17]. We hypothesized that individual electrodes would be better than generic electrode sites. Our first study of the executive attention network used the anterior cingulate along the frontal midline as the site of stimulation. We also wished to be able to determine if brain areas with lower intrinsic theta than the ACC would also show an increase in intrinsic theta by appropriate choice of electrodes and a task. To test these hypotheses we compared theta rhythm induced in the ACC and in the primary motor area by both generic and individual electrodes location. In each case choosing a cognitive task that also activates the chosen brain area. The results generally favor the use of individual electrodes particularly for the ACC location. Using individual electrode locations with electrical stimulation plus appropriate task we found significant increases in theta in both of the tested brain areas.

The next step in our plan will be to test our hypothesis that we can improve white matter in areas around the ACC. We will use 20 sessions of electrical stimulation plus task and compare before and after diffusion tensor imaging (DTI) to measure Fractional Anisotropy (FA) and calculate changes in g ratio as we have done in the mouse [18]. If our hypothesis of white matter change in the human brain was to be confirmed, we, or perhaps others, can use this method in actual clinical cases where white matter degeneration or loss is a likely cause of the abnormality.

CLINICAL APPLICATIONS

Our published work to date indicates that degree of white matter change is limited. In mice, the change in g ratio following a month of stimulation is about 5 percent [14]), and our MRI meditation studies have shown about 10 percent change in fractional anisotropy [12]. Moreover, the Attention Network Test is improved by training by approximately 10 percent of the improvement in reaction time found during development between 7 years and adulthood [19]. Thus, 10 percent may serve as an upper bound of the change we might expect. It is unclear whether a 10 percent change would be sufficient to improve disorders involving white matter, or whether it will provide benefits in skilled performance for those without such disorders.

Some published data favor the idea that addiction disorders might benefit from improved white matter. We [20] studied a group of smokers who showed reduced connectivity between the ACC and striatum when compared with a comparable group of non-smokers. The participants were recruited to reduce stress and did not necessarily have an intention to quit smoking. Nonetheless two weeks of meditation training improved connectivity and led to highly significantly reduction in smoking [20]. Although further tests are needed, the restoration of white matter efficiency appeared linked to reduced smoking.

In this paper, we have reviewed recent discoveries about the brain networks of attention, and the opportunities for rehabilitation they may make possible. Specific attentional networks based on imaging and neurophysiological research are being associated with the symptoms found with various neurological and psychiatric disorders (Table 2). There is little doubt that connections surrounding the anterior cingulate play a critical role in the voluntary control of emotions and thoughts [21,22].

Research in mice shows that low frequency stimulation can change white matter and reduce anxiety [14,15]. The intrinsic theta rhythm of the ACC can be increased by external electrical stimulation conducted while the person carries out the ANT [16]. We believe that other brain networks can also be modified in a similar manner. Methods are being explored to improve the functioning of these brain networks in animals and humans. We do not yet know whether or to what degree any of these methods will help to alleviate disorders related to white matter loss. However the current advances in this possibility support research designed to address whether they will work and what will work best.

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REFERENCES

1. Posner MI, Rothbart MK. Research on attention networks as a model for the integration of psychological science. Annu Rev Psychol. 2007;58:1–23.
2. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. Annu Rev Neurosci. 2012;35:71–89.
3. Posner MI, Rothbart MK, Sheese BE, Voelker P. Developing Attention: Behavioral and Brain Mechanisms. Adv Neuros-

ci (Hindawi). 2014;2014:405094.
4. Fan J, McCandliss BD, Sommer T, Raz M, Posner MI. Testing the efficiency and independence of attentional networks. J Cogn Neurosci. 2002;3(14):340–7.
5. Posner MI. Attention in a social world. New York: Oxford University Press; 2012.
6. Ghassemzadeh H, Rothbart MK, Posner MI. Mechanisms of response prevention and the use of exposure therapy for obsessive-compulsive disorder. International Journal of Psychiatry 2017;2/1 30 April 1-8.
7. Graybiel AM, Rauch SL. Toward a Neurobiology Review of Obsessive-Compulsive Disorder. Neuron. 2000;28:343-347
8. Ghassemzadeh H, Rothbart MK, Posner MI. Anxiety and Brain Networks of Attentional Control. Cogn Behav Neurol. Forthcoming.
9. Correia SS, McGrath AG, Lee A, Graybiel AM, Gossens KA. Amygdala- ventral striatum circuit activation decreases long-term fear. eLife. 2016;5:12669.
10. Kaczkurkin A, Park S, Soriras A, Sharma A, Moore T, et al. Association between Dimensional Fear and Cortical Thickness in Youth. Am J Psych. (in press).
11. Fjell AM, Walhovd K, Brown T, Kuperman J, Chung Y, Hagler D, et al. Multi-modal imaging of the self-regulating brain. Proc Natl Acad Sci USA. 2012;109:19620–5.
12. Tang Y, Lu Q, Geng X, Stein EA, Yang Y, Posner MI. Short term mental training induces white-matter changes in the anterior cingulate. Proc Natl Acad Sci USA. 2010;107:16649–52.
13. Xue S, Tang YY, Tang R, Posner MI. Short-term meditation induces changes in brain resting EEG theta networks. Brain Cogn. 2014;87:1–6.
14. Piscopo D, Weible A, Rothbart MK, Posner MI, Niell CM. Changes in white matter in mice resulting from low frequency brain stimulation. Proc Natl Acad Sci USA. 2018;115(27):6639–46.
15. Weible AP, Piscopo DM, Rothbart MK, Posner MI, Niell CM. Rhythmic brain stimulation reduces anxiety-related behavior in a mouse model based on meditation training. Proc Natl Acad Sci U S A. 2017;114(10):2532-2537.
16. Voelker P, Parker AN, Luu P, Davey C, Rothbart MK, Posner MI. Comparing methods to improve intrinsic theta in the anterior cingulate. Dev Cogn Neurosci. submitted.
17. Luu P, Essaki Arumugam EM, Anderson E, et al. Slow-Frequency Pulsed Transcranial Electrical Stimulation for Modulation of Cortical Plasticity Based on Reciprocity Targeting with Precision Electrical Head Modeling. Front Hum Neurosci. 2016;10:377. Published 2016 Aug 2. doi:10.3389/fnhum.2016.00377
18. Stikov N, Perry LM, Pauly JM, Wandell BA, Dougherty RF. Modeling and Measuring the Myelin g-ratio Proceedings International. Soc Magn Reson Med. 2011;19:225.
19. Voelker P, Rothbart MK, Posner MI. A polymorphism related to methylation influences attention during performance of speeded skills. AIMS Neurosci. 2016;3(1):40–55.
20. Tang YY, Tang R, Posner MI. Brief meditation training induces smoking reduction. Proc Natl Acad Sci U S A. 2013;110(34):13971–5.
21. Boord P, Madhyastha TM, Askren MI, Grabowski TJ. Executive attention networks show altered relationship with default mode network in PD NeuroImage. Clinical. 2017;13:1–8.
22. Darby RR, Joutsa J, Burke MJ, Fox MD. Lesion, network localization of free will. Proc Natl Acad Sci U S A. 2018 Oct 16;115(42):10792-10797. doi: 10.1073/pnas.1814117115.