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Answers to queries

1. key words: attention networks, alerting, orienting, neuromodulators, temperament, genetic variation

2. Data accessibility OK

3.

Ref 5. Should be

Rothbart, M. K., & Derryberry, D. (1981a). Development of individual differences in temperament. In M. E. Lamb & A. L. Brown (Eds.), *Advances in developmental psychology* (Vol. 1, pp. 37–86). Hillsdale, NJ: Erlbaum.

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Rothbart, M. K., & Bates, J. E. (2006). Temperament. In W. Damon, R. Lerner, & N. Eisenberg (Eds.), *Handbook of child psychology, Sixth edition: Social, emotional, and personality development* (Vol. 3, pp. 99–106). New York: Wiley.

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Rothbart, M. K., & Rueda, M. R. (2005). The development of effortful control. In U. Mayr, E. Awh, & S. W. Keele (Eds.), *Developing individuality in the human brain: A tribute to Michael I. Posner* (pp. 167–188). Washington, DC: American Psychological Association

4.

Ref 7 New York, New York USA:Scientific American Books

5. Omit reference 50

6. No update at this time. It will be submitted in January 2018 to PNAS

Insert A

In this issue Robbins point out how neuromodulators function within specific circuits or networks, making a further contribution to the network approach.

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Opinion piece



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Author for correspondence:

Michael I. Posner
e-mail: mposner@oregon.uoregon.edu

Temperament and brain networks
of attention

Michael I. Posner and Mary K. Rothbart

Department of Psychology, University of Oregon, Eugene, OR, USA

MIP, 0000-0002-7060-987X

The attention networks of the human brain are important control systems that develop from infancy into adulthood. While they are common to everyone, they differ in efficiency, forming the basis of individual differences in attention. We have developed methods for measuring the efficiency of these networks in older children and adults and have also examined their development from infancy. During infancy the alerting and orienting networks are dominant in control of the infant's actions, but later an executive network dominates. Each network has been associated with its main neuromodulator and these have led to associations with genes related to that network neuromodulator. The links between parent reports of their child's effortful control and the executive attention network allow us to associate molecular mechanisms to fundamental behavioural outcomes.

This article is part of the theme issue 'Diverse perspectives on diversity: multi-disciplinary approaches to taxonomies of individual differences'.

1. Introduction

It is now generally agreed that attention refers to a number of different functions and brain networks [1–3]. Moreover, most writers agree on the importance of neurochemical modulators in the operation of these networks. Trofimova & Robbins [3] have outlined a framework for relating neurochemical modulators to temperament that considers three major temperamental traits: orientation, speed of integration and maintenance of behaviour. As pointed out in Table 1 of their paper, these views overlap with our effort to understand how attention is carried out by brain networks, and how individual differences in attention constitute dimensions of temperament. We have defined temperament as constitutionally based individual differences in reactivity and self-regulation [4,5]. In this opinion piece, we outline how our framework might provide a useful perspective for understanding how individual differences should be regarded in the study of brain mechanisms.

The idea of brain networks related to psychological functions goes back at least to Hebb [6], but has received more emphasis as neuroimaging has revealed that many human tasks are orchestrated by a number of widely separate brain areas and their connections [7]. Although many brain networks (e.g. those involved in attention and memory) are common to all people, differences among individuals exist in the efficiency of these networks. These differences may involve synaptic mechanisms, the efficiency of white matter connections or biochemical transmission or modulation.

2. Attention networks

Our studies have divided attention into three networks [8]. These involve obtaining and maintaining the alert state, orienting to sensory stimuli and executive control of voluntary behaviour. Phasic changes in alertness are induced by warning signals, while orienting involves cues that tell the person where a target will occur. Executive attention is most frequently measured by the time to resolve conflict. The most common tasks for inducing conflict are the flanker task and Stroop task. Imaging [9] has revealed the mostly separate neural areas involved in each of

these networks. The network approach has been expanded into studies of brain development following the discovery that many networks are active during rest [10]. Resting state MRI studies and graph theory have been used to trace the connectivity among brain areas, including a fronto-parietal network (orienting) and a cingulo-opercular (executive) network, from infancy to adulthood [11–13]. By comparing resting state studies with developmental studies of specific attention networks [14,15], it is possible to obtain a greatly enlarged view of the separation and integration of brain areas underlying attention during development.

3. Measurement

We have used ~~two~~ quite different methods to examine individual differences in these networks. The first method involves measuring the efficiency of each network within a single cognitive task requiring a speeded response. The Attention Network Task (ANT) [14] uses the well-known flanker task [16] and provides cues to the time or location of the target. Subtractions of reaction times allow a measure for each network. This task can be used in various versions with children of 4 years and older as well as adults of any age. The scores, representing the efficiency of each network, are mainly independent [14], although there are significant correlations under some conditions [17]. Moreover, the same flanker task used in the ANT has been shown to depend upon the size of the anterior cingulate cortex (ACC) during early childhood [15].

The second method is the use of parent-report questionnaires and laboratory observations of infant and child temperament [4,18]. We have found, for example, that effortful control, a higher level self-regulation factor from questionnaire data that is also assessed in the laboratory (e.g. [19]), correlates with the difference between congruent and incongruent flankers in the ANT [20]. The ability to relate a cognitive task to parent reports of their child's effortful control has allowed a wide range of important observations. Effortful control has been shown to be related to the ability of parents to train their children in prosocial behaviour [19]. Using a combined measure of parent-, teacher- and child-report and observer ratings taken between 3 and 11 years, Moffitt *et al.* [21] found that childhood self-control (control of attention, action and emotion) predicted critical adult outcomes such as income, health and social relations more than 20 years later. Thus, network efficiency as measured by the ANT can be related to significant behavioural differences, further supporting efforts to understand the mechanisms underlying self-regulation.

4. Molecular mechanisms

One aspect of the ANT is measurement of orienting by use of cues that direct the organism to the location of the target. This measure of the ANT has been widely used in animal research with rodents and primates [22–24]. One study using these cues found that injections of NE antagonists such as clonidine or guanfacine to rats blocked the improvement in RT from cues indicating that a target would be presented (alerting), but did not alter the improvement in RT from cues that directed the rat's attention to a particular location (orienting). On the other hand, injecting antagonists to Ach blocked improvement from knowing where the target would occur, but had no effect on RT improvement from warning signals

[22]. Other studies, mainly with primates, have shown that orienting is carried out by ventral and dorsal parts of the parietal lobe, together with the frontal eye fields and subcortical areas [23]. Although it is well known that neuromodulators can influence each other and that their effects are not independent [3], these findings show that specific effects of individual modulators can be shown for simple task components. There is also evidence that the nicotinic Ach has important effects on orienting [25] and that NE is largely influential with respect to alertness [3].

If particular attention networks are associated with specific neuromodulators it becomes possible to test the idea that those genes are related to attention in predictable ways. To do this we have used genes with frequent polymorphisms, finding that genes related to NE affect alerting but not orienting as measured by the ANT, while genes related to Ach influence orienting but not alerting [26–28]. It has also been shown that dopamine and serotonin have effects on the time to resolve conflict [27–29]. This work provides a useful framework for determining what genes are related to which networks.

5. Genes and development

The work cited in the last section is with adults, and our studies of infants and children provide links to later attention networks. To examine this, we carried out a longitudinal study from seven months to 7 years [27,30]. We found that several genes related to attention were in early life related to temperamental factors of positive and negative affect [31]. We also found that early parent reports of affective temperament were related to later attention network performance. For example, infants' positive affect predicted the child's speed at resolving conflict at 7 years, and infants' perceptual sensitivity predicted 7-year-old children's alerting. Finally, the infant's approach tendencies predicted later orienting [27,28]. This finding supports relations between early temperament and later attention networks, although more longitudinal research is needed. We do not know whether early temperament is only a predictor of later attentional networks or whether temperament assessed in infancy is somehow instrumental in the development of these networks. However, the gene \times environment interactions described below suggest an important role for parenting in shaping the child's temperament.

Part of the relation between early temperament and later attention network measures rests on genetic variability, but substantial evidence exists also for experience as found in gene \times environment interactions. As one example, we found that impulsivity, a key temperament factor in Attention Deficit Disorder, was related to aspects of the quality of parenting, but only for those children with a version of the dopamine 4 receptor gene which had seven repeats of a particular 48 bp [32]. Our finding showed that the seven repeat was needed for a correlation between parenting quality and the temperament trait of impulsivity. A different study [33] assigned children with the seven repeat and those without the seven repeat randomly to a programme of parental training. The parent training intervention was effective in reducing impulsivity, but only for those children with the seven repeat allele, thus showing that the seven repeat is a cause of differences in behaviour related to the intervention.

The importance of brain networks of attention in early behaviour is reinforced by the finding that the alerting and

orienting networks are present very early in development. During infancy, parents work to obtain control of attention through such devices as presenting novel objects. These not only attract the infant's attention and serve to aid soothing [34], but are also likely to activate frontal areas related to the executive network, possibly aiding in executive attention development. The executive networks in adults involve separate areas of the anterior cingulate that provide control of emotion and cognition [35,36].

6. Interventions

Two types of intervention have been developed to improve attention. One form is called network training; it involves training on a particular cognitive task or computerized game. A second form of training, called state training, involves reaching a brain state that will foster attention and self-regulation, such as aerobic exercise [37] or mindfulness meditation [38].

Many studies of training the executive network have been carried out in children [39–41]. Computerized exercises designed to improve conflict resolution have been used [40,41], or more general school curricula have been designed to exercise multiple aspects of executive functions [39]. Both kinds of studies have demonstrated an improvement in executive attention [39] as well as some transfer [40,41]. The issue of how far generalization of network training can extend to other tasks has been controversial. Successful generalization of network training methods has been reported more consistently for very young participants [40,41] and for the elderly [42], with less evidence for generalization among young adults. Since these studies use different tasks and different training methods, it is still too early to draw strong conclusions about the training methods that can work best at different ages.

One form of state training involves mindfulness meditation. This type of meditation training involves a set of mental practices designed to achieve control over the direction of one's attention by either focusing on a specific content

(e.g. one's breathing or a word), or keeping a relaxed state in which attention is not allowed to wander but is not focused on a particular content. Consistent structural changes found in a meta-analysis of meditation studies [43] are in the ACC and insula, parts of the executive attention network [1]. A series of studies of mindfulness meditation have used random assignment and a relaxation control condition to test the influence of training [44,45]. These studies found evidence of white matter changes surrounding the ACC, along with improved executive attention and lowered stress [44–46]. We hypothesized that meditation could cause changes in white matter through the mediation of the increased frontal theta found following meditation training [28,47]. To test this idea, we used a mouse model in which rhythmic activity was imposed on the ACC for 20 days. When compared with unstimulated controls, the low-frequency stimulation produced a reduction in anxiety [48] and increased the number of oligodendrocytes related to myelination of connections [49].

7. Summary

Our attention framework provides a natural way to relate brain networks of attention common to all people with individual differences in their efficiency. Attention is a part of the early temperament of the infant and continues to control cognition and affect as the organism develops. This framework has also provided links between levels of analysis from the molecular mechanisms of white matter change to important outcomes of adult life.

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Competing interests. We have no competing interests.

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Q2

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