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:TITLE: Mental retardation and developmental disabilities research reviews.
:IMPRINT: New York, NY : Wiley-Liss, 1995-
:ARTICLE: Author: Davidson RJ and Slagter HA Article Title: Probing emotion in the developing brain: functional neuroimaging in the assessment of the neural substrates of emotion in normal and disordered children and adolescents
:VOL: 6 :NO: :DATE: 2000 :PAGES: 166-170 PT
:VERIFIED: OCLC ISSN: 1080-4013 [Format: Serial]
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MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES RESEARCH REVIEWS 6: 166–170 (2000)

PROBING EMOTION IN THE DEVELOPING BRAIN: FUNCTIONAL NEUROIMAGING IN THE ASSESSMENT OF THE NEURAL SUBSTRATES OF EMOTION IN NORMAL AND DISORDERED CHILDREN AND ADOLESCENTS

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Virtually all developmental neuropsychiatric disorders involve some dysfunction or dysregulation of emotion. Moreover, many psychiatric disorders with adult onset have early subclinical manifestations in children. This essay selectively reviews the literature on the neuroimaging of affect and disorders of affect in children. Some critical definitional and conceptual issues are first addressed, including the distinctions between the perception and production of emotion and between emotional states and traits. Developmental changes in morphometric measures of brain structure are then discussed and the implications of such findings for studies of functional brain activity are considered. Data on functional neuroimaging and childhood depression are then reviewed. While the extant data in this area are meager, they are consistent with studies in adults that have observed decreased left-sided anterolateral prefrontal cortex activation in depression. Studies in children on the recognition of emotion and affective intent in faces using functional magnetic resonance imaging are then reviewed. These findings indicate that the amygdala plays an important role in such affective face processing in children, similar to the patterns of activation observed in adults. Moreover, one study has reported abnormalities in amygdala activation during a task requiring the judgment of affective intent from the eye region of the face in subjects with autism. Some of the methodological complexities of developmental research in this area are discussed, and directions for future research are suggested.

MRDD Research Reviews 2000;6:166–170.

Key Words: emotion; affective neuroscience; affective style; functional neuroimaging; development; amygdala; prefrontal cortex

Virtually all psychiatric disorders involve some dysfunction or dysregulation of affect including anxiety and mood disorders as well as schizophrenia [Davidson et al., 1999]. Moreover, most psychiatric disorders of childhood such as autism and attention deficit hyperactivity disorder (ADHD) also involve abnormalities in the processing or production of emotion. Many psychiatric disorders that have full-blown onsets in the young adult years have early subclinical manifestations in childhood [e.g., Biederman et al., 1993]. These early occurring, more subtle expressions of the antecedents of later-emerging disorders might be associated with functional impairments in brain activity that can be detected early in life using modern neuroimaging techniques.

DEFINITIONAL AND CONCEPTUAL ISSUES IN THE STUDY OF EMOTION, AFFECTIVE STYLE, AND AFFECTIVE DISORDERS IN A DEVELOPMENTAL CONTEXT

A crucial distinction to make at the outset is between the perception of emotional information and the production of emotion. Most extant research using neuroimaging has utilized paradigms that involve the perception of emotional information such as facial expressions. A smaller corpus of data has explicitly targeted the production of emotion [see Davidson, 1993; 1998 for an extended discussions of this issue]. One important complication in developmental research is that stimuli used to probe the perception of emotional information in adults (e.g., facial expressions) may be more likely to elicit emotion in children compared with adults. For example, the presentation of a fear face to an adult is unlikely to actually evoke much emotion, while in a young child, there is an increased likelihood that such a stimulus could provoke emotion. Thus, the clear separation between the perception and production of emotion may be more complicated in children compared with adults. At the very least, it is important for investigators to remain sensitive to this issue and ideally to acquire other dependent measures that would permit an evaluation of the extent to which emotion was actually recruited by the stimulus manipulations used in a particular study. For example, we have used both emotion-mod-

Grant sponsor: NIMH; Grant number: K05-MH00875 (to RJD). Grant sponsor: NIMH; Grant number: P50-MH52354 (to RJD).

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ulated startle and facial electromyography to verify the presence of an intended emotion [Sutton et al., 1997]. These procedures can easily be used with neuroimaging methods to ascertain the extent to which emotion might actually be recruited.

Another important issue in this literature is the distinction between emotional states and traits [Ekman and Davidson, 1984]. There are several issues worth noting in this context. First, there are stable individual differences in measures of brain electrical activity from prefrontal scalp regions that are related to aspects of affective style. Affective style is a phrase that Davidson [1992; 1998] has used to characterize valence-specific features of individual differences in emotional reactivity. These individual differences have been observed in infants [Davidson and Fox, 1989] and children [Fox, 1991] and have been found to predict age-relevant behavioral measures of negative and positive emotional reactivity. One crucial issue for research in this area is the extent to which these individual differences are stable over time in the first decade or so of life. There are some data that strongly suggest that these features of brain activity are not stable in childhood [Davidson and Rickman, 1999], despite the impressive evidence for stability found later in life [Tomarken et al., 1992]. The extent to which these conclusions are borne out with other, more spatially precise hemodynamic neuroimaging methods is unclear and requires further study. However, we have recently reported excellent test-retest stability in adults of measures of regional glucose metabolism derived from positron emission tomography using MRI-based anatomical regions of interest in subcortical regions that are emotion-relevant [Schaefer et al., 2000]. Again, whether instability of these trait-like indices in children, similar to that observed in measures of brain electrical activity, is an issue that has not yet been addressed in the literature.

The issues noted above call for longitudinal studies of brain activity in circuitry relevant to emotion beginning at early ages. Such studies would enable investigators to determine when robust stability emerges in emotion-related features of brain activity. Moreover, they would enable the determination of whether small subgroups of children might show stability in patterns of abnormal brain activity from very early in life and whether such patterns predict anxiety, mood, or attention-related disorders later in childhood and early adulthood. Of course, this would require concurrent measures of affective behavior and symptoms, so that individual differences and developmental changes in brain activity could be systematically related to both concurrent and prospective behavioral and clinical indices.

DEVELOPMENTAL CHANGES IN BRAIN STRUCTURE: IMPLICATIONS FOR FUNCTIONAL NEUROIMAGING

Morphometric studies of relative gray and white matter volume in children and adolescents are of importance for the interpretation of results from functional neuroimaging studies in young subjects. Volumetric measures of developmental changes in regional brain structure are helpful for the interpretation of any developmental functional data because some variance in functional activity might arise as a consequence of morphometric changes over time. There are few studies that have investigated these developmental changes in the healthy child brain, and only one longitudinal study of this kind. In general, the data suggest differences both of total brain volume and of certain subcortical structures in children when compared to adults [e.g. Caviness et al., 1996; Giedd et al., 1996; 1999].

Of equal importance is the study of developmental changes in baseline cerebral blood flow (CBF) and metabolism. These values have been well established for adults [e.g., Frakowiak et al., 1980] but not for children. Results from PET studies in children suggest that both regional CBF and glucose metabolism increase after infancy, reaching a peak around the age of six to seven years, and then gradually declines toward adult levels during adolescence [Chugani et al., 1986; 1987; Chiron et al., 1992; Takahashi et al., 1999]. The relationship between age-related changes in baseline CBF and metabolism and age-related changes in measures of task-induced activation has not been systematically examined. Moreover, the coupling between neural activity and hemodynamic response might itself change with age. D'Esposito et al. [1999] found that some aspects of the coupling between neural activity and hemodynamic response was different in young (mean age: 22.9 years) versus older (mean age: 71.3 years) subjects. The extent to which there are age-related differences in this coupling mechanism early in life has also not been systematically investigated.

Giedd et al. [1996] used MRI to quantify temporal lobe, superior temporal gyrus, amygdala, and hippocampal volumes in 99 healthy children and adolescents aged 4–18 years. An enormous variability in size was observed for all structures. After correction for a 9% larger total cerebral volume in males, no significant volume differences between sexes were observed; however, sex-specific maturational changes were found. While total temporal lobe volume was stable, the right hippocampus increased significantly only in females, and left amygdala volume increased significantly only in males. Furthermore, a greater right-than-left asymmetry was observed for the temporal lobe, superior temporal gyrus, amygdala, and hippocampus.

In a recent study that included longitudinal assessment of almost half of a sample of 145 subjects using sophisticated image analysis methods, Giedd et al. [1999] reported, contrary to their earlier report, that temporal lobe gray matter volume showed nonlinear developmental changes with a maximum volume around 16 years of age followed by a slight decline. Frontal and parietal regions showed a similar nonlinear developmental pattern though with peaks at earlier ages (frontal and parietal cortical regions peaking at around 12 years of age for males and between 10 and 11 years of age for females), while the occipital region increased linearly from age 4 to 22 years.

In a related study, Thompson et al. [2000] used a tensor mapping strategy to characterize dynamic local growth patterns by performing repeat scans on young normal subjects at intervals ranging from two weeks to four years. Peak growth rates were observed in children between the ages of three and six years in the frontal circuits of the corpus callosum, with local growth during that time period ranging from 60% to 80%. Growth in the fiber systems that mediate various aspects of language function grew more rapidly than surrounding tissue before and during puberty, then dropped off rapidly.

The functional significance of these developmental morphometric changes for emotional or cognitive development is unclear. Speculations about connections between particular normative developmental milestones and observed changes in regional brain volume are hazardous at best. At the very least, it will be important to actually measure the emotional or cognitive processes of interest and also obtain MRI morphometric measures in the same individuals. Only in this way can meaningful associations between behavior and morphometric changes be established. In one re-

cent attempt to connect age-related differences in functional brain activation with developmental changes in motor inhibition and timing, Rubia et al. [2000] compared nine normal adolescents (mean age = 15 years) with eight normal adults (mean age = 29 years) on both performance measures and fMRI measures of regional brain activation during task performance. While this study asked a number of other questions, of most significance for this discussion are their data showing that in the delay task, adults outperformed adolescents, and there was greater activation in a fronto-striato-parietal circuit in the adults compared with the adolescents. While this study did not include morphometric measures, it did attempt to connect age-related differences in task performance with age-related differences in regional patterns of activation. What we do not know from this study is whether the differences in activation between the two groups are at least in part a function of morphometric differences between them.

However, even in the absence of these data, it is important to emphasize the methodological import of developmental changes in regional brain morphometry. Young males and females appear to differ in the age at which the growth curves peak for regionally-selective areas of gray matter [see also Caviness et al., 1996], underscoring the importance of taking gender into account in functional neuroimaging studies. It also should be noted that most "pediatric" neuroimaging studies have used only one age group, and very few studies have explicitly had a developmental focus. As more of these types of studies are performed, the necessity of combining structural and functional data will become more apparent.

NEURAL BASES OF CHILDHOOD DEPRESSION: EVIDENCE FROM FUNCTIONAL NEUROIMAGING

There are few studies that have examined hemodynamic measures of brain function in depressed children. Here we review these studies and suggest strategies for probing the neural bases of affective dysfunction in childhood depression. In a study that used single photon emission computed tomography (SPECT) to image regional cerebral blood flow (rCBF) with technetium-99m-HMPAO, Tutus et al. [1998] examined 14 adolescent patients with a major depressive disorder (MDD) (mean age: 13.11 years, range: 11–15 years) and 11 age-matched healthy controls. The purpose was to correlate changes in cerebral perfusion with clinical state and to study the possible association between rCBF and severity of symptomatology, duration of illness, and length of current depressive episode. While control subjects were scanned only once, depressed patients were scanned twice: under nonmedicated conditions and approximately six weeks later under medication, after depressive symptoms had subsided. The relative perfusion index (PI) was calculated as the ratio of regional cortical activity to whole brain activity. This index was used as an indicator of brain region perfusion changes. In addition, an asymmetry index (AI) was calculated for each region of interest based on the right-left difference divided by the sum of right and left [i.e., $(R-L)/(R+L)$]. Relatively reduced perfusion was observed in the unmedicated depressed patients compared with the healthy controls in the left anterofrontal and left temporal areas. Relative left anterofrontal rCBF also was shown to be reduced in the patient group during their depressed phase in comparison to during remission. Furthermore, the depressed state had a greater right-left hemispheric perfusion asymmetry compared with the controls. No differences were found between patients in remission and the normal subjects. This might indicate that the observed abnormalities in brain perfusion in patients in their depression are state, instead of trait, dependent markers for adolescent MDD. No significant correlation was obtained between perfusion changes and any of the clinical variables.

The pattern of left anterolateral hypoactivation in the patients is consistent with the literature on adult depression [see Davidson, 1998; Davidson and Irwin, 1999 for review]. While some studies have found these effects to be state-dependent in adults as Tutus et al. [1998] have found with adolescents, others have reported more trait-like asymmetry differences that persist during periods of remission [e.g., Henriques and Davidson, 1990; Allen et al., 1993].

Another SPECT study with a smaller sample of patients [Kowatch et al., 1999] found a different constellation of differences between depressed adolescents and controls. The depressed subjected showed relative rCBF decreases in the left parietal lobe, the anterior thalamus, and the right caudate as compared to healthy controls. rCBF increases were found in the right medial temporal cortex (a region including the amygdala), the right superior-anterior temporal lobe, and the left infero-lateral temporal lobe in the depressed group as compared to the normal controls. It is difficult to make sense of these disparate findings other than to stress the small sample sizes and clinical heterogeneity of the subjects.

An important task for future research will be to more carefully assess both the overt clinical symptoms as well as obtain laboratory-based measures of emotional reactivity to examine in relation to the neuroimaging data. For example, in a recent report, we presented evidence showing that increases in glucose metabolic rate in the amgydala were apparent only among depressed patients who also had substantial elevations of negative affect as reflected in a standardized dispositional measure of this construct [Abercrombie et al., 1998].

A large corpus of behavioral and psychophysiological data is available on behavioral inhibition, a temperament style that can be measured in toddlers and young children, that is predicted to be associated with an increased risk for adult anxiety disorders [e.g., Kagan and Snidman, 1999]. Electrophysiological studies have suggested that this temperament style is associated with right-sided prefrontal activation [Fox, 1991; Davidson and Rickman, 1999; Kagan and Snidman, 1999]. Moreover, Kagan [1994] has speculated that this may be associated with a lowered threshold or increased reactivity of the amygdala. It is thus important, and now feasible, to test children who are selected as extreme on behavioral measures of inhibition, and ascertain whether they show increased activation of the amygdala in response to fear-evoking or aversive stimuli. In addition, Davidson et al. [in press] have suggested, on the basis of both animal and human studies, that the hippocampus may be involved in behavioral inhibition. Therefore, it would be of interest to examine differences between behaviorally inhibited and uninhibited children in fMRI measures of hippocampal activation in response to both cognitive and affective tasks that are known to activate the hippocampus [see Davidson et al., in press, for examples].

RECOGNITION OF EMOTION AND AFFECTIVE INTENT IN FACES: FMRI STUDIES

Baird et al. [1999] used fMRI to study facial affect recognition in healthy adolescents (n = 12, mean age 13.9, range 12–17 years) under three conditions. In the first, subjects were instructed to fixate on a point presented in the middle of the screen. During the second condition, pictures of fearful faces were shown. During the final condition, sub-

jects were presented with nonsense visual stimuli that were matched in size and intensity to the face pictures. For three regions of interest (ROIs), the left and the right amygdala and a control region in the superior parietal lobe, the functional images obtained during the different conditions were compared. The data from the left and right amygdala were combined as no differences in activation were observed between the two studies. The amygdala was shown to exhibit a significantly stronger response during presentation of the facial expression stimuli than during the point-fixation condition; the nonsense visual stimulus condition did not activate the amygdala. Moreover, significantly greater activation was found in the amygdala in response to recognition of fear faces compared to nonsense stimuli. As expected, no differences between conditions were observed in the control ROI in the superior parietal lobe. The results from this study resemble findings from similar studies with adults [see Davidson and Irwin, 1999 for review] and demonstrate limbic system activation in adolescents suggesting its involvement in affect recognition prior to adulthood. Developmental changes could not be properly addressed by this study, however, as the sample size was small and the age distribution skewed (with more older than younger adolescents).

In a study using adult autistic and nonautistic subjects (mean age approximately 25 years for both groups), Baron-Cohen and colleagues [Baron-Cohen et al., 1999] used fMRI to ascertain whether amygdala activation was present when subjects were required to judge what another person was feeling or thinking from a picture of their eyes—a putative measure of social intelligence. The control task involved presentations of the identical upper face stimuli while subjects were asked to make a gender discrimination. Control subjects showed activation of the superior temporal gyrus and amygdala during the social intelligence tasks, while the autistic subjects failed to show significant amygdala activation during these tasks.

IMPLICATIONS, METHODOLOGICAL CONUNDRUMS, AND FUTURE RESEARCH

We began by reviewing some of the definitional and conceptual issues in the study of emotion in a developmental context. It is clear that the literature on neuroimaging of childhood affective dysfunction is just beginning. However, there are some promising trends. First, there is now an impressive literature on morphometric changes in the brain over the course of early development. These data will help establish patterns of structure-function relations developmentally once behavioral and MR measures are obtained in the same subjects in a longitudinal fashion. In addition, these data will be crucial in the interpretation of any developmental differences found in functional neuroimaging.

Certain problems are common to all areas of developmental research or to other neuroimaging applications. For example, having equivalent tasks at different ages that tap age-appropriate expressions of a particular competence is an important issue for all developmental research. The only difference for neuroimaging studies is that the stimulus content and response requirements should be similar across ages so that any age-related differences can be attributed to developmental changes in the underlying process of interest and not artifacts of alterations in the mechanics of the task. A problem that is generic to neuroimaging studies is the strategy used to assess for asymmetric activation [Davidson and Irwin, 1999]. Many studies of affect are based upon hypotheses predicting asymmetric activations in certain brain regions, such as the prefrontal cortex. Unfortunately, the manner in which asymmetries are most often assessed in neuroimaging studies is to simply ascertain whether an activation occurred that exceeded threshold in one hemisphere and did not exceed threshold in the opposite hemisphere. The problem with this strategy is that we do not know if there is a significant Condition × Hemisphere or Group × Hemisphere interaction. An apparently asymmetric activation could arise because the activation in one hemisphere just exceeded statistical threshold while the activation in the opposite hemisphere fell just short of statistical threshold. While this would appear as an asymmetric response, it arises as a consequence of the arbitrary statistical threshold adopted and would not emerge as a significant interaction. While the interaction test is conceptually straightforward, it belies considerable conceptual and methodological complexity [see Davidson and Irwin, 1999].

In conclusion, we believe that the time is ripe to increase the utilization of functional neuroimaging, particularly fMRI to probe affective dysfunction in developmental disorders. fMRI is the first hemodynamic imaging method that can be used safely with children and has excellent spatial and temporal resolution. The cortical and limbic circuitry of emotion now can be interrogated using sophisticated behavioral tasks in conjunction with fMRI, and we can look forward to an increase in the use of these methods to study the devastating and often long-lasting consequences of childhood disorders of emotion. We also believe that the judicious use of these methods may enable us to better predict which children may be particularly at-risk for serious psychopathology, facilitating the earlier introduction of remedial interventions. ■

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