Smart on the Inside: Functionally Rich Differences in Connectivity Within the Dorsolateral Prefrontal Cortex Are Present in Early Infancy

Chiara Caldinelli (caldinec@tcd.ie)
Trinity College Institute of Neuroscience, Lloyd Institute
Dublin 2, Ireland

Laura Cabral (lcabral@uwo.ca)
The Brain and Mind Institute
London, Ontario N6A 3K7, Canada

Rhodri Cusack (rhodri@cusacklab.org)
Trinity College Institute of Neuroscience, Lloyd Institute
Dublin 2, Ireland

Abstract:

Outwardly, babies are not smart - humans demonstrate little in the way of goal-directed behaviour or intelligence during early infancy. But, this does not imply that they do not have covert executive functioning. To investigate this, rather than measuring behaviour, we used neuroimaging to examine the maturity of the network responsible for executive function and in particular its key hub, the dorsolateral prefrontal cortex (DLPFC). The DLPFC was recently divided in adults into 26 sub-regions. We find that in adults these sub-regions have distinctive signatures of connectivity with the rest of the brain, reflecting their functional specializations in cognitive tasks. In infants, we found that these distinctive signatures of connectivity were already present by a few months of age. This suggests that infants may be more capable of executive functions than previously thought.

Keywords: infant; tractography; prefrontal cortex

Introduction

Goal-directed behaviour and intelligence are critically important during childhood and adult life but their development is still poorly understood. The central challenge in measuring the emergence of complex cognition is that the tasks used in children and adults cannot be performed by preverbal infants as their behavioural repertoire is too limited, and it is not at all clear how the tasks could be adapted.

Here we take a different approach and use neuroimaging to measure the maturity of a region central to complex cognition, the dorsolateral prefrontal cortex (DLPFC, Barbey et al., 2013). A defining characteristic of the DLPFC is that it is a hub region that is richly connected (Cole et al, 2013), which likely facilitates its roles as a global workspace and in flexible attentional control (Dehaene et al., 1998). It is engaged by effortful tasks (Duncan et al., 2006) and to implement these higher cognitive abilities the DLPFC comprises a rich set of sub-regions, with a recent parcellation from the Human Connectome Project (HCP) identifying 26 sub-regions (Glasser et al., 2016).

Brain development has long been seen as a specialization from low-level (e.g., perceptual areas) to high-level regions (e.g., frontal areas; Gao et al, 2015). However, recent evidence suggests that the frontal lobes may be functionally active in neonates (Cusack et al., 2016; Dehaene-Lambertz et al., 2010, 2002; Doria et al., 2010; Smyser et al., 2010). High-level regions may be functioning to some degree, but it is not clear how mature they are. Our goal, therefore, was to examine the maturity in infants of the prefrontal cortex, focussing in particular on the hub of the DLPFC.

To assess the maturity of the DLPFC we examined the development of its sub-regions. In adults, the 26 sub-regions from the HCP have been found to have distinct profiles of brain activation during fMRI of different tasks, including mathematics, short-term memory, gambling, and language understanding (Glasser et al., 2016).

However, young infants cannot perform these tasks and it is not clear how they could ever be adapted, which precludes the use of fMRI. Therefore, instead we

built upon the close relationship between functional specialization and structural connectivity. Like in artificial neural networks, in the brain differences in connectivity track differences in function (Saygin et al., 2014; Smith et al., 2008). Furthermore, in childhood it is argued that the development of local functional specialization parallels the development of connectivity (Johnson et al, 2011; Cabral et al, submitted). We therefore measured the structural connectivity of the sub-regions of the DLPFC using diffusion-weighted MRI, which can be performed in infants without the need for a task.

First, in adults, we identified the aspects of connectivity of the sub-regions of the DLPFC that were predictive of their profiles of selectivity across fMRI tasks. We then used this adult model to evaluate whether the infant DLPFC has these functionally important variations in connectivity, allowing us to test if their anatomy could support rich adult-like profiles of functional activation across the sub-regions of the DLPFC.

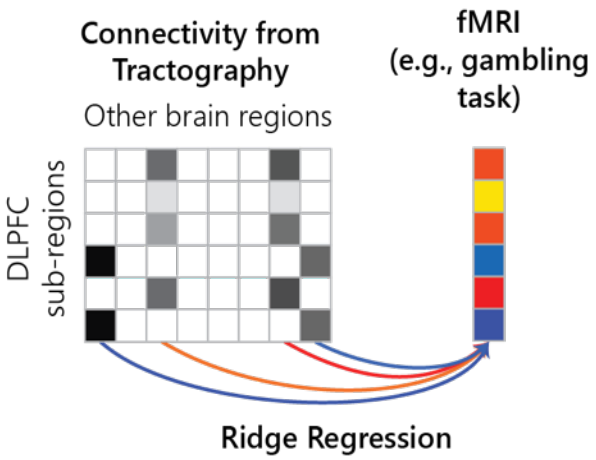

Figure 1: A ridge regression model was used to predict a sub-region's fMRI activation from its connectivity.

Methods

Image acquisition 14 adults and 11 infants (age 1-9 months, mean age=6.4 months) were scanned on a Siemens Prisma 3T at the Centre for Functional and Metabolic Mapping of Western University. Diffusion-weighted images (128 directions, voxel=2 mm^3, no gap, b=1500 mm s^{-2}, multiband factor of 4, two acquisitions with LR/RL phase encoding). Ethical approval was obtained from Western University's Health Sciences Research Ethics Board.

Image processing Diffusion data were analysed using probabilistic tractography with the FMRIB Toolbox (FDT v5.0; http://www.fmrib.ox.ac.uk/fsl). Voxels within the DLPFC (13 sub-regions in total per hemisphere, taken from the HCP), were used as seeds for tractography, and 334 regions elsewhere in the brain used as targets. fMRI contrasts capturing executive

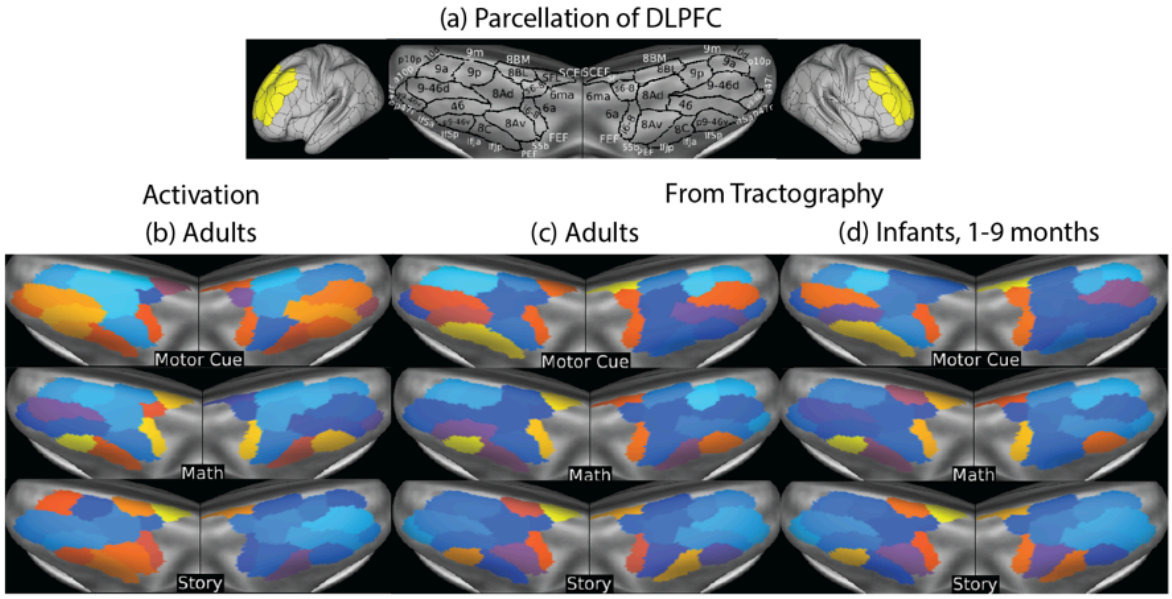

Figure 2: The connectivity pattern of sub-regions of the DLPFC (a) was sufficiently rich that fMRI activity across a wide range of tasks (b) could be recreated from connectivity in adults (c) and infants (d).

function, and a parcellation scheme, were also taken from the HCP (Glasser et al., 2016).

Statistical analysis We used three contrasts from three fMRI tasks to identify functionally important variation in connectivity between sub-regions. The tasks were: Motor Cue, Math, and Story (for a description of the tasks see [Barch et al., 2013]). Ridge regression was used to predict fMRI activation from tractography results (Fig. 1). This model was tested adults using leave-one-subject-out cross-validation. The maturity of connectivity in infants was then assessed using this adult model.

Results

In the adult group, for each of the three contrasts, the fMRI activation of a sub-region could be reliably recreated from its connectivity (Fig. 2, all r(25)=0.65-0.80, all p<0.001), which suggests that even at this scale, connectivity is strongly associated with function.

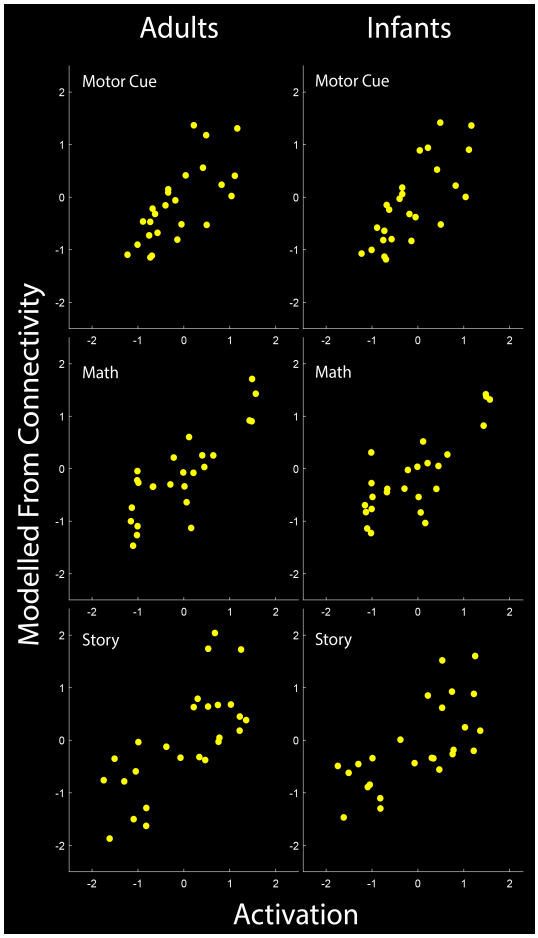

Figure 3: Results from tractography successfully recover fMRI activation (normalized z values are shown).

When this adult model was used with the infant patterns of connectivity, similar fMRI activation patterns were recovered (Fig. 3, all r(25)=0.55-0.80, all p<0.001).

Discussion

Our results from the adults show that the pattern of structural connectivity to the sub-regions of the DLPFC is sufficiently rich that it might account for the different profiles of activation across tasks.

The infant results suggest that as early as one month, the connectivity of sub-regions of the DLPFC is sufficiently mature that it could create adult-like patterns of fMRI activity. This suggests that higher-level cognitive functions like problem solving might not suddenly emerge as the brain matures, but could undergo a process of gradual development that begins soon after birth.

This adds to the growing evidence that even high-level cognitive systems are functional early in the first year (Cusack et al, 2014; Dehaene-Lambertz, 2015, 2010). It parallels recent evidence that the fronto-parietal network actively shapes early development, as its disruption by brain injury impacts motor learning by four months (Linke et al, 2018).

Future work will attempt to identify what functions of the DLPFC shape learning in the first years of life.

Acknowledgments

We thank: David Lee and Victor Han of London Health Sciences Centre, for assistance with recruitment; Hester Duffy, Charlotte Herzmann, Annika Linke, and Conor Wild for data acquisition, the Canada Excellence Research Chair (CERC) in Cognitive Neuroimaging, a Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant [NSERC 418293DG-2012], CIHR/NSERC Collaborative Health Research Project [CHRP 201110CPG] and the Children's Health Research Institute (to RC) from the Children's Health Foundation; and the families and infants who participated in this study.

References

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., Glasser, M. F., Curtiss, S., Dixit, S., Feldt, C., Bryant, E., Hartley, T., Footer, O.., Bjork, J., M., Poldrack, R., Smith, S.,

Johansen-Berg, H., Snyder, A., Z., Van Essen, D., C. (2013). Function in the human connectome: task-fMRI and individual differences in behavior. Neuroimage, 80, 169-189.

Barbey, A. K. (2013). Dorsolateral prefrontal contributions to human intelligence. Neuropsychologia, 51(7), 1361-1369.

Cabral, L., Zubiaurre, L., Wild, C., Linke, A., Cusack, R. Category-Selective Visual Regions Have Distinctive Signatures of Connectivity in Early Infancy. (Submitted)

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. Nature neuroscience, 16(9), 1348.

Cusack, R., Ball, G., Smyser, C. D. C. D., Dehaene-Lambertz, G. (2016) A Neural Window on the Emergence of Cognition. Annals of the New York Academy of Sciences 1369(1), 1–18.

Dehaene, S., Kerszberg, M., & Changeux, J. P. (1998). A neuronal model of a global workspace in effortful cognitive tasks. PNAS , 95(24), 14529-14534.

Dehaene-Lambertz, G., Dehaene, S. and Hertz-Pannier, L. (2002). Functional Neuroimaging of Speech Perception in Infants. Science 298 (5600), 2013–15.

Dehaene-Lambertz, G., Montavont, A., Jobert, A., Allirol, L., Dubois, J., Hertz-Pannier, L., & Dehaene, S. (2010). Language or music, mother or Mozart? Structural and environmental influences on infants' language networks. Brain and language, 114(2), 53-65

Dehaene-Lambertz, G., & Spelke, E. S. (2015). The infancy of the human brain. Neuron, 88(1), 93-109..

Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., Counsell, S. J., Murgasova, M., Aljabar, P., Nunes, R. G., Larkman, D J., Rees, G. & Edwards, D. (2010). Emergence of resting state networks in the preterm human brain. PNAS, 107(46), 20015-20020.

Duncan, John. 2006. EPS Mid-Career Award 2004: Brain Mechanisms of Attention. Quarterly Journal of Experimental Psychology , 59(1), 2–27.

Gao, W., Alcauter, S., Elton, A., Hernandez-Castillo, C. R., Smith, J. K., Ramirez, J., & Lin, W. (2014). Functional network development during the first year: relative sequence and socioeconomic correlations. Cerebral cortex, 25(9), 2919-2928.

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C. F., Jenkison, M. & Smith, S. M. (2016). A multi-modal parcellation of human cerebral cortex. Nature, 536(7615), 171-178.

Johnson, Mark H. (2011) Interactive Specialization: A Domain-General Framework for Human Functional Brain Development? Developmental Cognitive Neuroscience, 1(1), 7–21.

Linke, A.C., Wild, C., Zubiaurre-Elorza, L, Duffy, H., Herzmann, C., Han, V., Lee, D.S.C., & Cusack, R. (2018). Disruption to functional networks in neonates with perinatal brain injury predicts motor skills at 8 months. Neuroimage Clinical, 18, 399–406.

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A., R. & Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. PNAS, 106(31), 13040-13045.

Saygin, Z. M., Osher, D. E., Koldewyn, K., Reynolds, G., Gabrieli, J. D., & Saxe, R. R. (2012). Anatomical connectivity patterns predict face selectivity in the fusiform gyrus. Nature neuroscience, 15(2), 321.

Smyser, C. D., Inder, T. E., Shimony, J. S., Hill, J. E., Degnan, A. J., Snyder, A. Z., & Neil, J. J. (2010). Longitudinal analysis of neural network development in preterm infants. Cerebral cortex, 20(12), 2852-2862.