FORUM

ANOMALOUS LATERALISATION IN NEURODEVELOPMENTAL DISORDERS

Ester I. Klimkeit[1] **and John L. Bradshaw**[2]

([1]Monash University Centre for Developmental Psychiatry and Psychology, School of Psychology, Psychiatry and Psychological Medicine, Monash Medical Centre, Clayton, Victoria, Australia; [2]Department of Psychology, School of Psychology, Psychiatry, and Psychological Medicine, Monash University, Clayton, Victoria, Australia)

Lateralisation of brain structure, neurochemicals, emotionality, and function appears even in animals (e.g., Vallortigara et al., 1999). Right dopaminergic lateralisation in the rat's frontal cortex is associated with lower anxiety, and its lack to greater anxiety (Thiel and Schwarting, 2001). Gestational stress results in long-term changes of dopaminergic lateralisation, and in reduced hemispheric asymmetry (Fride and Weinstock, 1988). Emotional experiences differentially modify left and right brain neurochemistry, and the lateralisation of motor behaviour (Alonso et al., 1997).

Human neurodevelopmental disorders may stem from underdevelopment of normal hemispheric activity, or exaggeration of normal functional allocation. Anomalous lateralisation may, secondarily, impact on symptom expression. The genetic nature of neurodevelopmental disorders suggests a possible adaptive value. Thus, creativity associates with depression/mania, meticulous attention to detail with autism, and high energy and risk taking with attention deficit hyperactivity disorder (ADHD) (see Bradshaw, 2001). We review anomalous brain lateralisation in schizophrenia, ADHD, Tourette's syndrome (TS), depression, autism and obsessive compulsive disorder (OCD).

Depression

Left prefrontal lesions associate with depression, right hemisphere (RH) lesions with mania (Rogers et al., 1998). Neuroimaging studies indicating left hemisphere (LH) underactivity (Goodwin, 1997) concur with the emotionality literature: positive emotions involve greater left frontal activity and negative emotions greater right frontal activity (Davidson et al., 1990). Relative left frontal underactivity is thus consistent with lowered mood. Studies show decreased right posterior cortex activity in depression (Deldin et al., 2000).

Impaired verbal fluency (Landro et al., 2001), probably reflecting left prefrontal functioning, resolves with antidepressants (Trichard et al., 1995). Patients show reduced leftward biases in judgements of happiness (Kucharska-Pietura and David, 2003), and an abnormally large LH advantage for dichotic fused words (Pine et al., 2000). Increased right ear advantage on the dichotic fused word task also predicts good response to fluoxetine (Bruder et al., 1996).

Schizophrenia

Greater activation occurs in the left globus pallidus (Early, 1993), with increased left amygdala dopamine (Reynolds, 1983). Patients show left ventricular enlargement (De Lisi et al., 1992) and corresponding decreases within the left temporal lobe, amygdala, hippocampus/parahippocampal region (Cowell et al., 1999; Petty, 1999). Reductions of left planum temporale and left superior temporal gyrus correlate with severity of hallucinations and thought disorder (Barta et al., 1990; Shenton et al., 1992).

Reduced right ear advantage in dichotic listening (Bruder et al., 1995), greater omission of right visual field (RVF) targets (Tomer and Flor-Henry, 1989), difficulties shifting attention to the RVF (Bustillo et al., 1997), and slow rightwards movement preparation (Downing et al., 1998), all suggest abnormal LH functioning.

Tourette's Syndrome

Various left basal ganglia (BG) regions are smaller in patients, with loss of normal left greater than right asymmetry (Petersen et al., 1993). Reduced right caudate volume, left lateral ventricular volume and loss of normal lateral ventricular asymmetry occurs (Hyde et al., 1995). Reduced blood flow occurs in left sided BG structures (Moriaty et al., 1995).

Adult patients show reduced leftward biases in line bisection and turning tests (Yazgan et al., 1995). Pediatric patients bisect lines to the right of centre, like RH damaged left neglect patients (Sheppard et al., 2002). While normal children show no performance asymmetry in movement latency, TS children show slower movement preparation for unexpected right targets (Bradshaw and Sheppard, 2000).

Attention Deficit Hyperactivity Disorder

ADHD reflects right sided frontal striatal dysfunction (Heilman et al., 1991), with smaller right prefrontal cortices (Hill et al., 2003) and RH hypoarousal (Zametkin et al., 1990). Patients detect fewer left targets in letter cancellation (Voeller and Heilman, 1988), and bisect horizontal lines to the right of centre; methylphenidate normalises performance (Sheppard et al., 1999a). Increased cost of invalid cues for LVF targets also occurs in patients in visual orienting of attention tasks (Carter et al., 1995).

Autism

Right sided abnormalities are noted in the BG, frontal cortex (Buchsbaum et al., 1992) and right anterior cingulate (Haznedar et al., 1997). Muller et al. (1999, 1998) found reduced left prefrontal, left thalamus, and right dentate nucleus activation in patients during language tasks, and reversed language dominance. Siegel et al. (1992) found higher metabolic rate in left inferior frontal cortex and lower metabolic rate in left posterior putamen in sustained attention tasks. Blood flow is lower in the left temporal and parietal lobes, and higher in left frontal and occipital lobes (Hashimoto et al., 2000).

It has been suggested that pragmatic language deficits and dysprosodies reflect RH dysfunction, while LH aspects of language (syntax and phonology) are not affected in autism (Ozonoff and Miller, 1996). Movement disturbances occur, particularly on the right side (Teitelbaum et al., 1998), and RVF deficiencies occur in serial choice reaction time and visual orienting of attention tasks (Rinehart et al., 2002).

Obsessive Compulsive Disorder

Lacerda et al. (2003a) found higher cerebral blood flow in right superior and inferior frontal cortices of medication free individuals. Greater symptom severity correlated with higher blood flow in the right BG, while greater illness duration correlated with greater blood flow in the right thalamus. Increased right caudate nucleus volume also occurs (Scarone et al., 1992), and treatment response associates with reduced right caudate activity (Baxter et al., 1992). Obsessional state increases blood flow in the right caudate nucleus (Rauch et al., 1994). Perseverative errors associate with greater OCD severity and increased right thalamus activity (Lacerda et al., 2003b). Reduced inhibition of return for left targets suggests RH dysfunction (Rankins et al., 2004).

Conclusion

Neuroimaging and neuropsychological evidence suggests anomalous lateralisation in neurodevelopmental disorders. LH abnormalities occur in depression, schizophrenia and TS, and RH abnormalities in ADHD, autism and OCD. Differential involvement of the lateralised neurotransmitter systems (Bradshaw, 2001), characterise these disorders. Neurotransmitter distribution is asymmetrical: the LH is dominated by cholinergic and dopaminergic systems, and the RH by serotonergic and noradrenergic systems (Cicchetti and Toth, 1995). This lateralisation of the psychogenic amines reflects an evolutionary ancient, lateralised, arousal system. While TS may be associated primarily with dopaminergic dysfunction, OCD is probably associated with serotonergic dysfunction, and ADHD with noradrenergic and dopaminergic dysfunction (Sheppard et al., 1999b).

The fact that frontostriatal neurodegenerative disorders (Parkinson's and Huntington's disease) show largely normal lateralisation (Bradshaw, 2001), suggests that anomalous lateralisation in the frontostriatal neurodevelopmental disorders may reflect developmental compromise, at different stages and different regions, of the unfolding, maturing neurotransmitter system (Sowell et al., 2004). The different neurodevelopmental disorders may reflect differential compromise in time and place.

References

Alonso SJ, Navarro E, Santana C and Rodriguez M. Motor lateralization, behavioral despair and dopaminergic brain asymmetry after prenatal stress. *Pharmacology Biochemistry and Behavior, 58:* 443-448, 1997.

Barta PE, Pearlson GD, Powers RE, Richards SS and Tune LE. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *American Journal of Psychiatry, 147:* 1457-1462, 1990.

Baxter LR, Schwartz JM, Bergamon KS, Szuba MP, Guze BH, Mazziota JC, Alazraki A, Selin CE, Ferng HK, Munford P and Phelps ME. Caudate glucose metabolic rate change with both drug and behavior therapy for obsessive-compulsive disorder. *Archives of General Psychiatry, 49:* 681-689, 1992.

Bradshaw JL. *Developmental Disorders of the Frontostriatal System: Neuropsychological, Neuropsychiatric, and Evolutionary Perspectives*. Philadelphia: Psychology Press, 2001.

Bradshaw JL and Sheppard DM. The neurodevelopmental frontostriatal disorders: Evolutionary adaptiveness and anomalous lateralization. *Brain and Language, 73:* 297-320, 2000.

Bruder GE, Otto MW, McGrath PJ, Stewart JW, Fava M, Rosenbaum JF and Quitkin FM. Dichotic listening before and after fluoxetine treatment for major depression: Relations of laterality to therapeutic response. *Neuropsychopharmacology, 15:* 171-179, 1996.

Bruder GE, Rabinowicz E, Towey J, Brown A, Kaufmannn DA, Amador X, Malaspina D and Gorman JM. Smaller right ear (left hemisphere) advantage for dichotic fused words in patients with schizophrenia. *American Journal of Psychiatry, 152:* 932-935, 1995.

Buchsbaum MS, Siegel BV, Wu JC, Hazlett E, Sicotte N, Haier R, Tanguay P, Asarnow R, Carorette T, Donoghue D, Lagunas-Solar M, Lott I, Paek J and Sabalesky D. Brief report: Attention performance in autism and regional

brain metabolic rate assessed by positron emission tomography. *Journal of Autism and Developmental Disorders, 22:* 115-125, 1992.

BUSTILLO JR, THAKER G, BUCHANAN RW, MORAN M, KIRKPATRICK B and CARPENTER WT. Visual information-processing impairments in deficit and non-deficit schizophrenia. *American Journal of Psychiatry, 154:* 647-654, 1997.

CARTER CS, KRENER P, CHADERJIAN M, NORTHCUTT C and WOLFE V. Asymmetrical visual-spatial attentional performance in ADHD: Evidence for a right hemispheric deficit. *Biological Psychiatry, 37:* 789-797, 1995.

CICCHETTI D and TOTH SL. Developmental psychopathology and disorders of affect. In Cicchetti D and Cohen DJ (Eds), *Developmental Psychopathology: Risk, Disorder, and Adaptation*. New York: Wiley, 1995.

COWELL PE, FITCH RH and DENENBERG VH. Laterality in animals: Relevance to schizophrenia. *Schizophrenia Bulletin, 25:* 41-62, 1999.

DAVIDSON RJ, EKMAN P, SARON CD, SENULIS JA and FRIESEN WV. Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology I. *Journal of Personality and Social Psychology, 58:* 330-341, 1990.

DELDIN PJ, KELLER J, GERGEN JA and MILLER GA. Right-posterior face processing anomaly in depression. *Journal of Abnormal Psychology, 109:* 116-121, 2000.

DE LISI LE, HOFF AL, KUSHNER M, CALEV A and STRITZKE P. Left ventricular enlargement associated with diagnostic outcome in schizophreniform disorder. *Biological Psychiatry, 32:* 199-210, 1992.

DOWNING ME, PHILLIPS JG, BRADSHAW JL, VADDADI KS and PANTELIS C. Cue dependent right hemineglect in schizophrenia: A kinematic analysis. *Journal of Neurology, Neurosurgery and Psychiatry, 65:* 454-459, 1998.

EARLY T. Left globus pallidus hyperactivity and right-sided hemineglect in schizophrenia. In Cromwell RL and Snyder CR (Eds), *Schizophrenia: Origins, Processes, Treatment and Outcome*. New York: Oxford Press, 1993.

FRIDE E and WEINSTOCK M. Prenatal stress increases anxiety related behavior and alters cerebral lateralization of dopamine activity. *Life Sciences, 42:* 1059-1065, 1988.

GOODWIN GM. Neuropsychological and neuroimaging evidence for the involvement of frontal lobes in depression. *Journal of Psychopharmacology, 11:* 115-122, 1997.

HASHIMOTO T, SASAKI M, FUKUMIZU M, HANAOKA S, SUGAI K and MATSUDA H. Single-photon emission computed tomography of the brain in autism: Effect of the developmental level. *Pediatric Neurology, 23:* 416-420, 2000.

HAZNEDAR MM, BUCHSBAUM MS, METZGER M, SOLIMANDO A, SPIEGEL-COHEN J and HOLANDER E. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. *American Journal of Psychiatry, 154:* 1047-1050, 1997.

HEILMAN KM, VOELLER KK and NADEAU SE. A possible pathophysiologic substrate of attention deficit hyperactivity disorder. *Journal of Child Neurology, 6:* S76-S81, 1991.

HILL DE, YEO RA, CAMPBELL RA, HART B, VIGIL J and BROOKS W. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology, 17:* 496-506, 2003.

HYDE TM, STACEY ME, COPPOLA R, HANDEL SF, RICKLER KC and WEINBERGER DR. Cerebral morphometric abnormalities in Tourette's syndrome: A quantitative MRI study of monozygotic twins. *Neurology, 45:* 1176-1182, 1995.

KUCHARSKA-PIETURA K and DAVID AS. The perception of emotional chimeric faces in patients with depression, mania and unilateral brain damage. *Psychological Medicine, 33:* 739-745, 2003.

LACERDA ALT, DALGALARRONDO P, CAETANO D, CAMARGO EE, ETCHEBEHERE ECSC and SOARES JC. Elevated thalamic and prefrontal regional cerebral blood flow in obsessive-compulsive disorder: A SPECT study. *Psychiatry Research: Neuroimaging, 123:* 125-134, 2003a.

LACERDA ALT, DALGALARRONDO P, CAETANO D, HAAS GL, CAMARGO EE and KESHAVAN MS. Neuropsychological performance and regional cerebral blood flow in obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacological and Biological Psychiatry, 27:* 657-665, 2003b.

LANDRO NI, STILES TC and SLETVOLD H. Neurological function in nonpsychotic unipolar major depression. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 14:* 233-240, 2001.

MORIATY J, COSTA DC, SCHMITZ B, TRIMBLE MR, ELL PJ and ROBERTSON MM. Brain perfusion abnormalities in Gilles de la Tourette's syndrome. *British Journal of Psychiatry, 167:* 249-254, 1995.

MULLER RA, BEHEN ME, ROTHERMEL RD, CHUGANI DC, MUZIK O, MANGNER TJ and CHUGANI HT. Brain mapping of language and auditory perception in high-functioning autistic adults: A PET study. *Journal of Autism and Developmental Disorders, 29:* 19-31, 1999.

MULLER RA, CHUGANI DC, BEHEN ME, ROTHERMEL RD, MUZIK O, CHAKRABORTY PK and CHUGANI HT. Impairment of dentato-thalamo-cortical pathway in autistic men: Language activation data from positron emission tomography. *Neuroscience Letters, 245:* 1-4, 1998.

OZONOFF S and MILLER JN. An exploration of right-hemisphere contributions to the pragmatic impairments in autism. *Brain and Language, 52:* 411-434, 1996.

PETERSEN B, RIDDLE M, COHEN DJ, KATZ LD, SMITH JC, HARDIN MT and LECKMAN JF. Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. *Neurology, 43:* 941-949, 1993.

PETTY RG. Structural asymmetries of the human brain and their disturbance in schizophrenia. *Schizophrenia Bulletin, 25:* 121-137, 1999.

PINE DS, KENTGEN LM, BRUDER GE, LEITE P, BEARMAN K, MA Y and KLEIN RG. Cerebral laterality in adolescent major depression. *Psychiatry Research, 93:* 135-144, 2000.

RANKINS D, BRADSHAW JL, MOSS S and GEORGIOU-KARISTIANIS N. Inhibition of return in obsessive-compulsive disorder. *Journal of the International Neuropsychological Society, 10:* 54-59, 2004.

RAUCH SL, JENIKE MA, ALPERT NM, BAER L, BREITER CR, SAVAGE CR and FISCHMAN AJ. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labelled carbon dioxide and positron emission tomography. *Archives of General Psychiatry, 51:* 62-70, 1994.

REYNOLDS GP. Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. *Nature, 305:* 527-529, 1983.

RINEHART NJ, BRADSHAW JL, BRERETON AV and TONGE BJ. Lateralization in individuals with high-functioning autism and Asperger's disorder: A frontostriatal model. *Journal of Autism and Developmental Disorders, 32:* 321-332, 2002.

ROGERS MA, BRADSHAW JL, PANTELIS C and PHILLIPS JG. Frontostriatal deficits in unipolar major depression. *Brain Research Bulletin, 47:* 297-310, 1998.

SCARONE S, COLOMBO C, LIVIAN S, ABBRUZZESE M, RONCHI P, LOCATELLI M, SCOTTI G and SMERALDI E. Increased right caudate nucleus size in obsessive-compulsive disorder: detection with magnetic resonance imaging. *Psychiatry Research: Neuroimaging, 45:* 115-121, 1992.

SHENTON ME, KIKINIS R, JOLESZ FA, POLLACK SD, LEMAY M, WIBLE CG, HOKAMA H, MARTIN J, METCALF D, COLEMAN M and MCCARLEY RW. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. *New England Journal of Medicine, 327:* 604-612, 1992.

SHEPPARD DM, BRADSHAW JL and MATTINGLEY JB. Abnormal line bisection judgements in children with Tourette's syndrome. *Neuropsychologia, 40:* 253-259, 2002.

SHEPPARD DM, BRADSHAW JL, MATTINGLEY JB and LEE P. Effects of stimulant medication on the lateralisation of line bisection judgments of children with attention deficit hyperactivity disorder. *Journal of Neurology, Neurosurgery, and Psychiatry, 66:* 57-63, 1999a.

SHEPPARD DM, BRADSHAW JL, PURCELL R and PANTELIS C. Tourette's and comorbid syndromes: Obsessive compulsive and attention deficit hyperactivity disorder. A common etiology? *Clinical Psychology Review, 19:* 531-552, 1999b.

SIEGEL BV, ASARNOW R, TANGUAY P, CALL JD, ABEL L, HO A, LOTT I and BUCHSBAUM MS. Regional cerebral glucose metabolism and attention in adults with a history of childhood autism. *Journal of Neuropsychiatry and Clinical Neurosciences, 4:* 406-414, 1992.

SOWELL ER, THOMPSON PM and TOGA AW. Mapping changes in the human cortex throughout the span of life. *Neuroscientist, 10:* 372-392, 2004.

TEITELBAUM P, TEITELBAUM O, NYE J, FRYMAN J and MAURER RG. Movement analysis in infancy may be useful for early diagnosis of autism. *Proceedings of the National Academy of Sciences, 95:* 13982-13987, 1998.

THIEL CM and SCHWARTING RKW. Dopaminergic lateralisation in the forebrain: Relations to behavioural asymmetries and

anxiety in male Wistar rats. *Neuropsychobiology, 43:* 192-199, 2001.

TOMER R and FLOR-HENRY P. Neuroleptics reverse attention asymmetries in schizophrenic patients. *Biological Psychiatry, 25:* 852-860, 1989.

TRICHARD C, MARTINOT JL, ALAGILLE M, MASURE MC, HARDY P, GINESTET D and FÉLINE A. Time course of prefrontal lobe dysfunction in severely depressed in-patients: A longitudinal neuropsychological study. *Psychological Medicine, 25:* 79-85, 1995.

VALLORTIGARA G, ROGERS LJ and BISAZZA A. Possible evolutionary origins of cognitive brain lateralization. *Brain Research Reviews, 30:* 164-175, 1999.

VOELLER KKS and HEILMAN KM. Attention deficit disorder in children: A neglect syndrome? *Neurology, 38:* 806-808, 1988.

YAZGAN MY, PETERSON B, WEXLER BE and LECKMAN JF. Behavioral laterality in individuals with Gilles de la Tourette's syndrome and basal ganglia alterations: A preliminary report. *Biological Psychiatry, 8:* 65-74, 1995.

ZAMETKIN AJ, NORDAHL TE, GROSS M, KING AC, SEMPLE WE, RUMSEY J, HAMBURGER S and COHEN RM. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *The New England Journal of Medicine, 323:* 1361-1366, 1990.

Ester I. Klimkeit, Monash University Centre for Developmental Psychiatry and Psychology, School of Psychology, Psychiatry and Psychological Medicine, Monash Medical Centre, Clayton, Victoria 3168, Australia.
e-mail: Ester.Klimkeit@med.monash.edu.au