

6. Scalabrino G, Nicolini G, Buccellato FR, et al. Epidermal growth factor as a local mediator of the neurotrophic action of vitamin B₁₂ (cobalamin) in the rat central nervous system. *FASEB J* 1999;13:2083–2090.
7. Peracchi M, Bamonti Catena F, Pomati M, et al. Human cobalamin deficiency: alterations in serum tumour necrosis factor- α and epidermal growth factor. *Eur J Haematol* 2001; 67:123–127.
8. Heaton EB, Savage DG, Brust JCM, et al. Neurologic aspects of cobalamin deficiency. *Medicine* 1991;70:229–245.
9. Roos D. Neurological complications in patients with impaired vitamin B₁₂ absorption following partial gastrectomy. *Acta Neurol Scand* 1978;59(suppl 69):1–77.
10. Stabler SP, Allen RH, Barrett RE, et al. Cerebrospinal fluid methylmalonic acid levels in normal subjects and patients with cobalamin deficiency. *Neurology* 1991;41:1627–1632.
11. Blom HJ, Wevers RA, Verrips A, et al. Cerebrospinal fluid homocysteine and the cobalamin status of the brain. *J Inher Metab Dis* 1993;16:517–519.
12. Bottiglieri T. Folate, vitamin B₁₂, and neuropsychiatric disorders. *Nutr Rev* 1996;54:382–390.
13. Scalabrino G, Buccellato FR, Tredici G, et al. Enhanced levels of biochemical markers for cobalamin deficiency in totally gastrectomized rats: uncoupling of the enhancement from the severity of spongy vacuolation in spinal cord. *Exp Neurol* 1997; 144:258–265.
14. Egleton RD, Davis TP. Bioavailability and transport of peptides and peptide drugs into the brain. *Peptides* 1997;18:1431–1439.
15. Tracey KJ, Cerami A. Tumor necrosis factor, other cytokines and disease. *Annu Rev Cell Biol* 1993;9:317–343.
16. Yamada M, Ikeuchi T, Hatanaka H. The neurotrophic action and signalling of epidermal growth factor. *Prog Neurobiol* 1997;51:19–37.
17. Plata-Salamán CR. Epidermal growth factor and the nervous system. *Peptides* 1991;12:653–663.
18. Gutierrez EG, Banks WA, Kastin AJ. Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. *J Neuroimmunol* 1993;47:169–176.
19. Pan W, Kastin AJ. Entry of EGF into brain is rapid and saturable. *Peptides* 1999;20:1091–1098.
20. Gianazza E, Veber D, Eberini I, et al. Cobalamin (vitamin B₁₂)-deficiency-induced changes in the proteome of rat cerebrospinal fluid. *Biochem J* 2003;374:239–246.

Learning to Read without a Left Occipital Lobe: Right-Hemispheric Shift of Visual Word Form Area

Laurent Cohen, MD, PhD,^{1,2}
Stéphane Lehericy, MD, PhD,³ Carole Henry, MD,^{1,2}
Marie Bourgeois, MD,⁴ Christine Larroque, MS,⁴
Christian Sainte-Rose, MD,⁴ Stanislas Dehaene, PhD,²
and Lucie Hertz-Pannier, MD, PhD⁵

Using anatomical and functional magnetic resonance imaging, we studied the pattern of brain lateralization during spoken and written language tasks, in an 11-year-old girl who underwent a left occipitotemporal resection for a Sturge–Weber angioma at the age of 4 years, that is, after the development of speech but before the acquisition of reading. We observed a selective and successful shift to the right hemisphere of the visual component of reading, particularly the Visual Word Form Area, whereas the verbal components remained strongly left-lateralized. This emphasizes the potential utility of a precise functional and developmental cartography of language for the surgical treatment of focal brain lesions in children.

Ann Neurol 2004;56:890–894

Left-hemispheric lesions occurring during early childhood are often compatible with a satisfactory language development,¹ even after complete hemispherectomy,^{2,3} illustrating the right hemisphere's potential to sustain most aspects of language, provided that compensation occurs early enough.^{3,4} Nevertheless, in children with focal left-hemispheric lesions, language lateralization is almost unpredictable,⁵ because of the intricate mutual links that constrain the development and lateralization of the distributed set of language-related brain modules.

Reading may constitute a simple and informative case on the dissociable lateralization of language mod-

From the ¹Institut de Neurologie, Hôpital de la Salpêtrière, AP-HP, Paris; ²Institut National de la Santé et de la Recherche Médicale U562, Service Hospitalier Frédéric Joliot, Commissariat à l'Énergie Atomique/Département des Sciences de la Vie, Orsay; ³Service de Neuroradiologie, Hôpital de la Salpêtrière; ⁴Service de Neurochirurgie Pédiatrique, Hôpital Necker; and ⁵Service de Radiologie Pédiatrique, Hôpital Necker, AP-HP, Paris, France.

Received Jun 7, 2004, and in revised form Sep 1. Accepted for publication Sep 16, 2004.

Published online Nov 24, 2004, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20326

Address correspondence to Dr Cohen, Service de Neurologie 1, Hôpital de la Salpêtrière, 47/83 Bd de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: laurent.cohen@psl.ap-hop-paris.fr

ules. Reading may be broken down into two components that are distinct from functional, anatomical, and developmental points of view. First, during the acquisition of reading, the visual system develops an ability to recognize letter strings in a fast and parallel fashion, invariant for changes in case, font, size, or position.⁶ This ability involves the Visual Word Form Area (VWFA), in the midportion of the left occipitotemporal sulcus,⁶ which encodes, in adult readers, the abstract identity of strings of visual letters. This system reaches its adult properties by the age of 10 years,^{7,8} although it is already left-lateralized by the age of 7 years.⁹ In adults, destruction¹⁰ or deafferentation¹¹ of the VWFA results in pure alexia. Second, children learn how to translate letter strings into phonological and lexical representations subtended by left perisylvian language areas. Left-hemispheric predominance for speech processing is discernible during the first months of life¹² and is a major factor of functional organization by the age of 8 to 10 years.^{13,14} The observation of deep dyslexia after left-hemispherectomy at the age of 15 years¹⁵ suggests that once their lateralization is established, the phonological components of reading cannot be compensated by right-hemispheric structures.

Using anatomical and functional magnetic resonance imaging (MRI), we studied the pattern of lateralization during spoken and written language tasks in an 11-year-old girl who underwent left occipitotemporal resection at the age of 4 years, that is, after the development of oral speech but before the acquisition of reading.

Case Report

Medical History and Lesion Topography

The patient was an 11-year-old left-handed girl (Edinburgh score: -80%) with a history of Sturge-Weber disease, a condition responsible for unilateral occipital leptomeningeal angioma and secondary cortical dysfunction.¹⁶ Focal seizures appeared at the age of 8 months. The patient received clobazam and carbamazepine and remained seizure-free until the age of 4 years. Language and other cognitive abilities developed normally. At the age of 5 years, because of the recurrence of seizures, the patient underwent surgical resection of most of her left occipital lobe, extending into the temporal white matter. She was again seizure-free until the age of 10 years, allowing her to receive successful schooling, including the acquisition of proficient reading. After the relapse of seizures, a complementary superior occipital resection then was performed. However, seizures persisted and the imaging procedure reported here was performed to help further therapeutic decisions.

Spoken and written language production and com-

prehension were normal on clinical assessment. The patient had complete right hemianopia. She took 50 seconds to read aloud flawlessly a text of approximately 100 words, a performance within the lower range of normal adults. She was asked to read aloud rapidly a list of 165 familiar words, 3 to 9 letters in length.¹⁰ She made 2 of 165 minor errors. She had a mean correct latency of 720 milliseconds, with an average increase of 17 milliseconds per letter. Both the mean latency and the slope of the word length effect were 2.3 standard deviations above the mean of 9 normal adults with a full visual field.¹⁰

T1-weighted MRI showed that the resected volume included the occipital lobe, the posterior segment of the inferior and middle temporal gyri, and the white matter of the fusiform and parahippocampal gyri to about TC $Z = -40$ anteriorly (Fig 1). A patch of

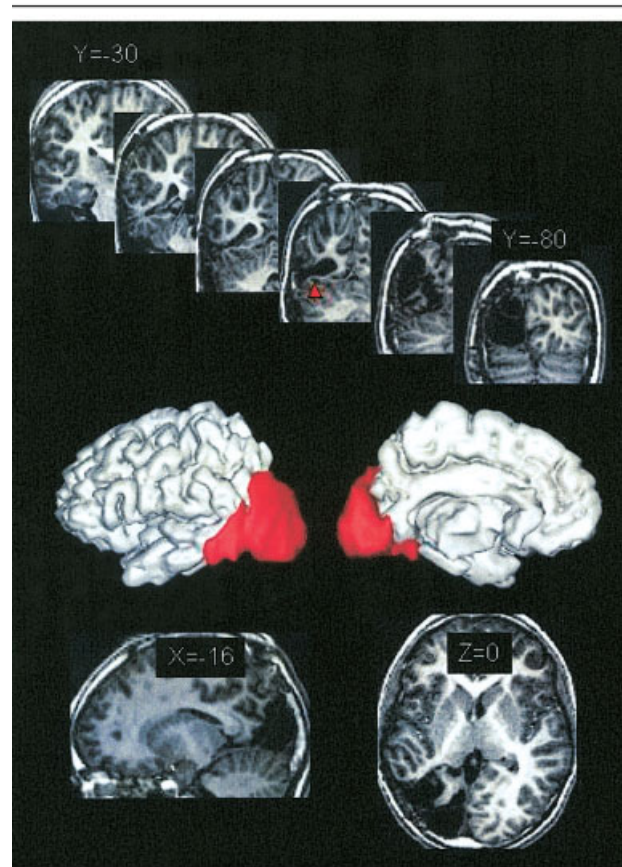


Fig 1. Brain slices and three-dimensional rendering of the patient's left hemisphere, normalized to Talairach space. The resected volume included the occipital lobe, only sparing the anterior precuneus, the posterior ITG and MTG, and the white matter of the fusiform and parahippocampal gyri to about TC $Z = -40$. A thin patch of cortex remained, covering this white matter resection, overlapping with the normal average position of the Visual Word Form Area (red arrowhead). ITG = inferior temporal gyrus, MTG = middle temporal gyrus.

disconnected ventral temporal cortex remained beneath the white matter resection, including the normal location of the VWFA.¹⁰

Functional Imaging

METHODS. The lateralization of oral language was studied using two functional MRI protocols.³ First, the patient was presented auditorily with concrete nouns, one every 5 seconds and was instructed to covertly generate a simple subject-verb-object sentence, using the target word as the object. As a control condition, the patient was asked to rest, while the word “rest” was presented every 5 seconds. Second, the patient was asked to listen to sentences, one every 5 seconds, each about 2.5 seconds long. She was asked to rest, with no stimulus presentation, as a control condition. For each protocol, the patient received two sequences, each comprising an alternation of four blocks of stimulation with four blocks of rest. Each block comprised five trials, yielding a total duration of 215 seconds for each sequence. The echo planar imaging acquisition was modified by grouping the slice acquisition on a 1.5-second period within each TR, leaving a silent interval of 3.5 seconds allowing for the presentation of auditory stimuli.

Word reading was studied using a protocol adapted from Cohen and colleagues.¹⁰ The patient was presented visually with blocks of words, checkerboards, or a fixation point. Stimuli were presented centrally for 1,000 milliseconds, followed by a 1,400-millisecond blank screen. The patient was instructed to pay equal attention to all types of stimuli and to covertly read the

words. She received three sequences, each comprising an alternation of four blocks of words, two blocks of checkerboards, and two blocks of fixation. Each block comprised 10 trials, yielding a total duration of 192 seconds for each sequence.

On each trial, one functional volume sensitive to blood oxygen level dependent contrast was acquired with a T2-weighted gradient echo, echo planar imaging sequence on a 1.5T Signa Imager (resolution= $5 \times 3.75 \times 3.75\text{mm}^3$). Four volumes were acquired at the beginning of each sequence to reach signal equilibrium and were discarded from the analyses.

Using the SPM99 software, functional images were realigned, normalized, and smoothed (5mm). Temporal filters were applied (high-pass at 240 seconds, low-pass Gaussian width 4 seconds). Activation on each type of trial was modeled by the Statistical Parametric Mapping hemodynamic function. Variables of noninterest modeled constant differences across sequences. We used a voxelwise threshold of *p* value less than 0.001 and a cluster-level threshold of *p* value less than 0.05 corrected.

Results

We first studied activations related to speech processing (Table; Fig 2). The subtraction of sentence perception minus baseline showed activation only in the left superior temporal gyrus (STG)/superior temporal sulcus (STS). The subtraction of sentence generation minus baseline showed left-sided activation in the dorsal and ventral Broca’s area, precentral cortex, supplementary motor area/cingulate, and STG/STS.

Table. Activated Areas during Oral Language Tasks and during Reading

Area	Voxel Z-Score	TC		
		<i>x</i>	<i>y</i>	<i>z</i>
Sentence perception > baseline				
Left superior temporal	7.10	-72	-24	-4
Sentence generation > baseline				
Left superior temporal	5.23	-72	-32	0
Broca’s area ventral	5.54	-56	8	4
Dorsal	6.31	-48	24	20
Left precentral	5.79	-60	4	32
Left SMA/cingulate	4.29	-36	4	48
Left SMA/cingulate	5.44	-12	12	44
Reading words > checkerboards				
Right ventral occipitotemporal	6.23	30	-90	-6
Right ventral occipitotemporal	4.77	36	-66	-12
Broca’s area ventral	5.58	-57	6	6
Dorsal	4.66	-45	33	12
Left precentral	5.25	-54	6	39
Right precentral	4.18	48	12	21
Left SMA/cingulate	5.98	-6	3	51
Left inferior parietal lobule	7.19	-36	-45	33
Left inferior parietal lobule	5.81	-54	-27	30

TC = Talairach coordinates; SMA = supplementary motor area.

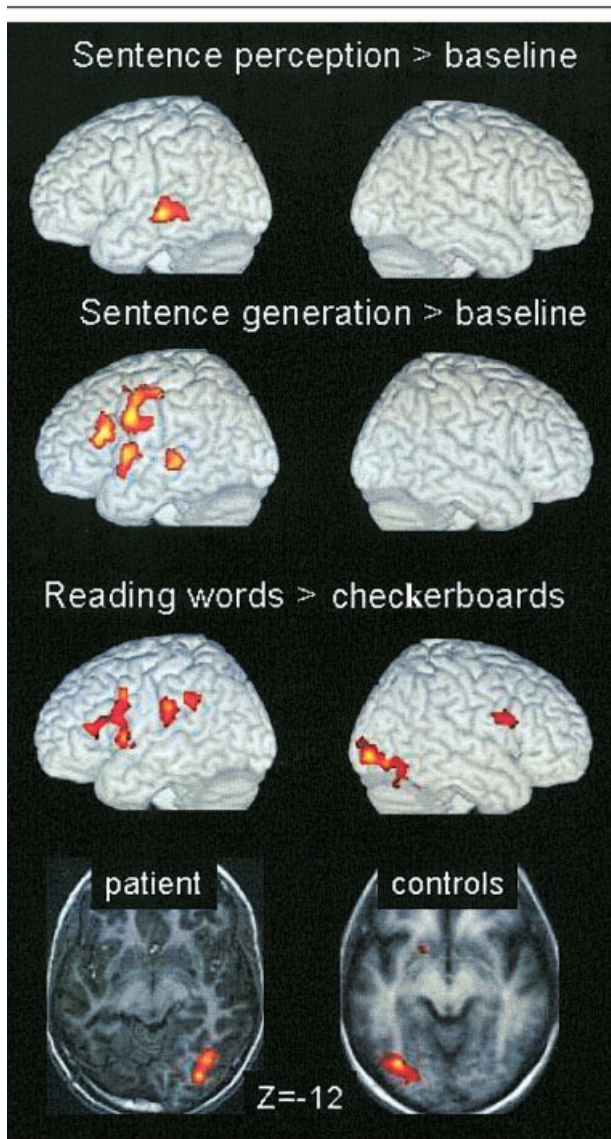


Fig 2. Activation of the patient's brain during sentence perception versus baseline (top row), sentence generation versus baseline (second row), word reading versus viewing checkerboards (third row). The activated frontal, superior temporal, and parietal language-related network was strongly left-lateralized. In the patient, occipitotemporal activation during reading was confined to the right hemisphere, whereas it is strongly left-lateralized in normal controls from Cohen and colleagues¹⁰ (bottom row). Statistical threshold: voxelwise $p < 0.001$ in the patient and $p < 0.01$ in controls (random effect group analysis); clusterwise $p < 0.05$.

To identify activations related to visual word processing, we contrasted word reading minus checkerboards, masking by the contrast of words minus fixation ($p < 0.001$). We observed activation in the left IPL, the left supplementary motor area/cingulate, ventral and dorsal Broca's area, bilateral precentral cortex, and the right ventral occipitotemporal cortex. The latter region extended anteriorly in the fusiform gyrus to

about TC $Z = -40$, including peaks almost exactly symmetrical to the classical location of the VWFA (normal subjects TC $-42 -57 -6$, ± 5 mm; present patient: TC $36 -66 -12$). No activation appeared in the residual left ventral temporal cortex, even at lower statistical thresholds, or when contrasting words minus fixation.

Discussion

We report the case of a child who underwent a left occipitotemporal resection at the age of 4 years but nonetheless developed normal reading abilities. The VWFA, which normally provides the input to subsequent stages of word reading, was not removed entirely but was deprived of visual input because of the underlying white matter resection. Beyond anatomical evidence (see Fig 1), the lack of activation during reading tasks demonstrated that this residual patch of cortex was not functional (see Fig 2). The symmetrical right-hemispheric region (R-VWFA) showed strong activation to words versus fixation, suggesting that it supported the function normally devoted to the VWFA. Moreover, the R-VWFA was activated more strongly by words than by checkerboards, a pattern that is restricted to the VWFA in most normal readers, whereas the R-VWFA is activated to a comparable level by both types of stimuli.¹⁰ The patient's R-VWFA thus was the necessary input pathway to her reading system, whereas in normal subjects, although activated, it is not required for normal reading, as demonstrated by the absence of alexia after right inferotemporal lesions. In contrast, all other language-related activations were strongly left-lateralized: Broca's area during covert speech generation, the superior temporal cortex during tasks involving speech perception, and the inferior parietal lobule during reading.

In sum, because the lesion occurred before the acquisition of literacy, there was a selective and successful shift to the right hemisphere of the visual component of reading, whereas verbal transcoding and output remained in the left hemisphere. This adaptation may have taken advantage of direct transcallosal projections from the right occipitotemporal cortex to the language areas.¹⁷ Note that a similar interhemispheric shift may operate in adults who develop letter-by-letter reading as a compensation strategy in pure alexia.^{10,11}

Finally, the demonstration with functional MRI of the absence of activation in the residual left ventral temporal cortex contributed to the decision to perform a further occipitotemporal resection. This led to a complete cessation of seizures, allowing the patient to resume normal schooling (11-year-old in sixth grade). This emphasizes the utility of a precise functional and developmental cartography of oral and written language for the surgical treatment of focal brain lesions in children.

References

1. Vargha-Khadem F, O'Gorman AM, Watters GV. Aphasia and handedness in relation to hemispheric side, age at injury and severity of cerebral lesion during childhood. *Brain* 1985;108:677–696.
2. Vargha-Khadem F, Isaacs E, Muter V. A review of cognitive outcome after unilateral lesions sustained during childhood. *J Child Neurol* 1994;9(suppl 2):67–73.
3. Hertz-Pannier L, Chiron C, Jambaque I, et al. Late plasticity for language in a child's non-dominant hemisphere: a pre- and post-surgery fMRI study. *Brain* 2002;125:361–372.
4. Muller RA, Rothermel RD, Behen ME, et al. Language organization in patients with early and late left-hemisphere lesion: a PET study. *Neuropsychologia* 1999;37:545–557.
5. Liegeois F, Connelly A, Cross JH, et al. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. *Brain* 2004;127:1229–1236.
6. McCandliss BD, Cohen L, Dehaene S. The Visual Word Form Area: expertise for reading in the fusiform gyrus. *Trends Cogn Sci* 2003;7:293–299.
7. Aghababian V, Nazir TA. Developing normal reading skills: aspects of the visual processes underlying word recognition. *J Exp Child Psychol* 2000;76:123–150.
8. Shaywitz BA, Shaywitz SE, Pugh KR, et al. Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biol Psychiatry* 2002;52:101–110.
9. Gaillard WD, Balsamo LM, Ibrahim Z, et al. fMRI identifies regional specialization of neural networks for reading in young children. *Neurology* 2003;60:94–100.
10. Cohen L, Martinaud O, Lemer C, et al. Visual Word Recognition in the left and right hemispheres: anatomical and functional correlates of peripheral alexias. *Cereb Cortex* 2003;13:1313–1333.
11. Cohen L, Henry C, Dehaene S, et al. The pathophysiology of letter-by-letter reading. *Neuropsychologia* 2004;42:1768–1780.
12. Dehaene-Lambertz G, Dehaene S, Hertz-Pannier L. Functional neuroimaging of speech perception in infants. *Science* 2002;298:2013–2015.
13. Balsamo LM, Xu B, Grandin CB, et al. A functional magnetic resonance imaging study of left hemisphere language dominance in children. *Arch Neurol* 2002;59:1168–1174.
14. Gaillard WD, Hertz-Pannier L, Mott SH, et al. Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology* 2000;54:180–185.
15. Patterson K, Vargha-Khadem F, Polkey CE. Reading with one hemisphere. *Brain* 1989;112:39–63.
16. Comi AM. Pathophysiology of Sturge-Weber syndrome. *J Child Neurol* 2003;18:509–516.
17. Di Virgilio G, Clarke S. Direct interhemispheric visual input to human speech areas. *Hum Brain Mapp* 1997;5:347–354.

In Vivo Detection of Microglial Activation in Frontotemporal Dementia

Annachiara Cagnin, MD,^{1,2} Martin Rossor, MD, FRCP,³ Elizabeth L. Sampson, MD,³ Toby MacKinnon, MBBS,¹ and Richard B. Banati, MD^{1,4,5}

Using positron emission tomography and [¹¹C](R)-PK11195, a marker of “peripheral benzodiazepine sites” that is upregulated on activated microglia during progressive tissue pathology, we show increased binding of [¹¹C](R)-PK11195 in frontotemporal lobar degeneration in the typically affected frontotemporal brain regions. This implies the presence of an active glial response reflecting progressive neuronal degeneration. It also suggests that increased [¹¹C](R)-PK11195 binding, previously demonstrated for Alzheimer's disease, may occur independently from increased amyloid plaque formation, given that it is not a characteristic feature of frontotemporal lobar degeneration.

Ann Neurol 2004;56:894–897

Frontotemporal lobar degeneration (FTLD) is characterized by focal atrophy of the temporal and frontal lobes.¹ Three main histopathological features are found: nonspecific changes of neuronal loss, microvacuolation, and gliosis; τ deposition including Pick bodies; and ubiquitin-positive, τ -negative inclusions.^{2,3} Glial changes including activated microglia are common, but, unlike Alzheimer's disease (AD), increased amyloid plaque formation is usually not seen.^{4,5}

The isoquinoline PK11195 is a ligand for the “peripheral benzodiazepine binding site” that is particularly abundant in cells of mononuclear-phagocyte lineage. High-resolution, single-cell, [³H](R)-PK11195 autoradiography combined with immunocytochemical

From the ¹MRC Cyclotron Unit, MRC Clinical Sciences Centre, Imperial College London, Hammersmith Hospital Campus, London, United Kingdom; ²Department of Neurosciences, University of Padova, Padova, Italy; ³Dementia Research Group, Institute of Neurology Queen Square, London, United Kingdom; ⁴Department of Neuropathology, Imperial College School of Medicine, Charing Cross Hospital, London, United Kingdom; and ⁵School of Medical Radiation Sciences and Ramaciotti Center for Brain Imaging (Brain Mind Research Institute), University of Sydney, Sydney, New South Wales, Australia.

Received Apr 26, and in revised form Aug 4 and Sep 30. Accepted for publication Sep 30, 2004.

Published online Nov 24, 2004, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20332

Address correspondence to Dr Banati, Chair of Medical Radiation Sciences, University of Sydney, East Street, PO Box 170, Lidcombe, New South Wales 1825, Australia. E-mail: r.banati@fhs.usyd.edu.au