CIEL-5, Chinese University of Hong Kong, 18 August, 2013

Brain mechanisms of reading:
Universal or Culture-specific?

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University of Hong Kong


kinesisk sprog sproglig videnskab og hjernen
Danish

Chinese Language,
Linguistic Science
and Brain

Langue Chinoise,
La linguistique science
et
Cerveau

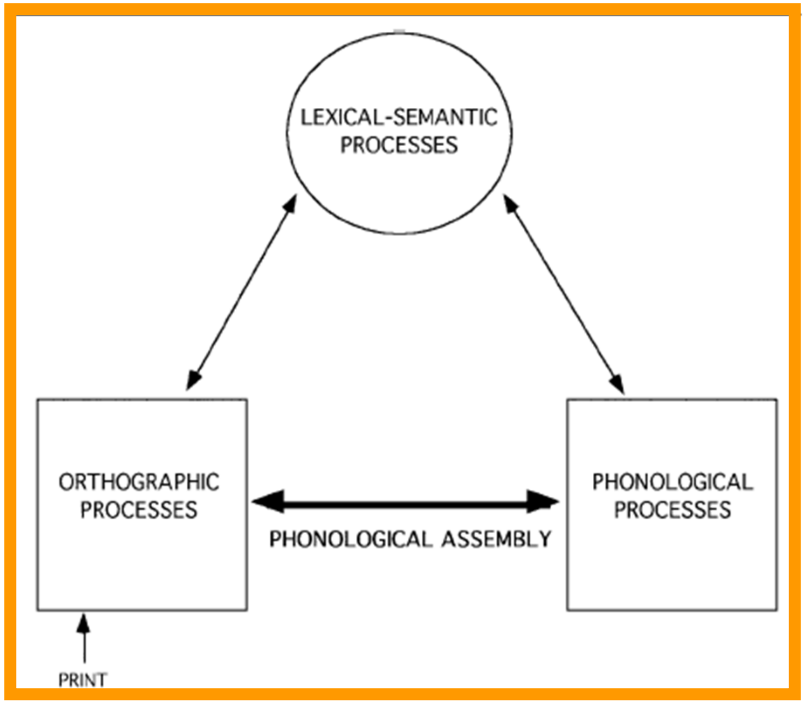
中国语文,
语言科学和脑

རྒྱ་སྐད་སྐད་བརྡ་རིག་པ།ཚན་རིག་དང་ཀླད་པ།

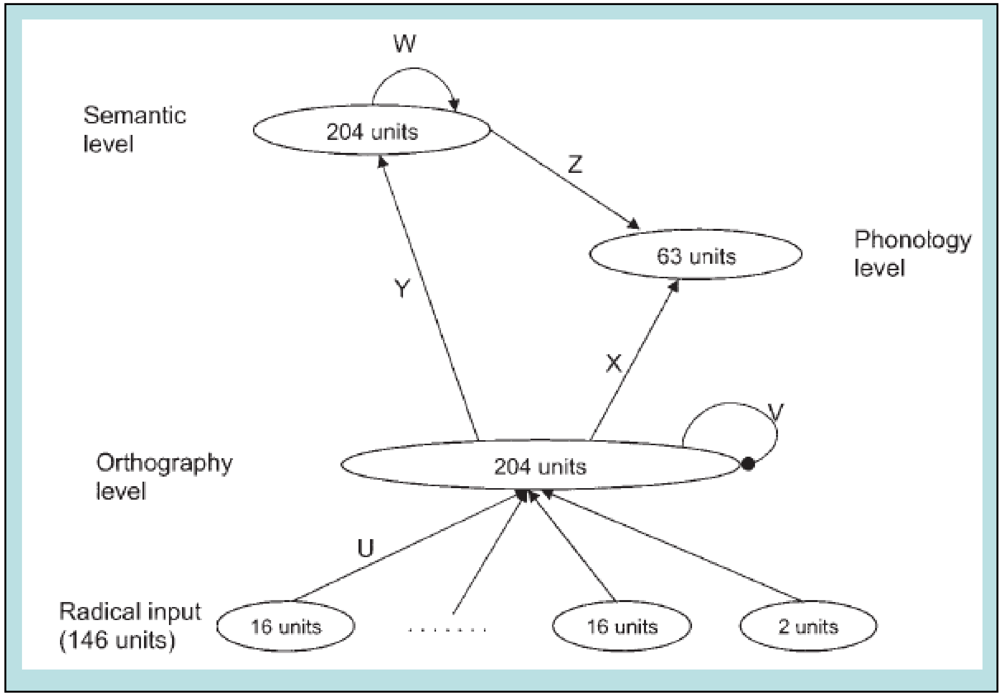
Visuo-orthography
Phonology
Semantics
Syntax

Common cognitive processes are entailed in reading development in all languages

Reading acquisition in all written languages depends on the establishment of effective connections among three linguistic elements: orthography, phonology, and semantics.



Pugh et al., 2000



Perfetti, Liu, & Tan, 2005

Neural Mechanisms of
Language and Reading:

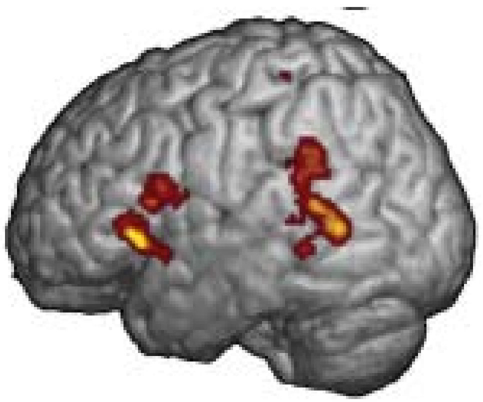
Are they universal or language-constrained?

The Universal Theory:
A universal brain basis is involved for reading in all languages

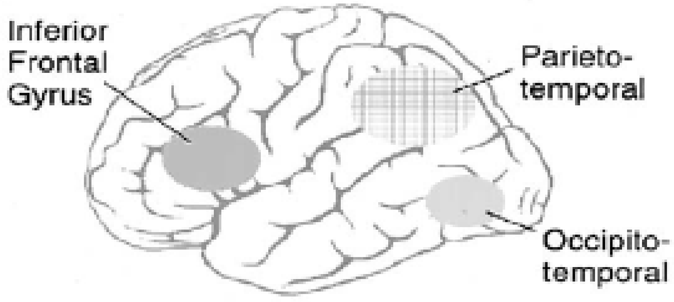
(Paulesu et al., Science, 2001; Dehaene et al., 2012)

Neuroimaging of normal and dyslexic reading in alphabetic languages: 3 systems

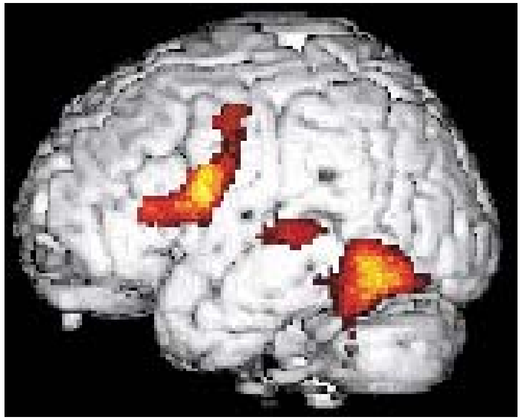
- **Visual word form area (fusiform gyrus): orthography**
- **Temporoparietal regions: phonological processing**
- **Inferior frontal gyrus: phonology and meaning**



Turkeltaub et al., 2003, English



Pugh et al., 2005
3 systems



Paulesu et al., 2001, English
French & Italian

Recent functional neuroimaging findings of dyslexia in alphabetic languages

Flower et al. (1991)

Rumsey et al. (1992)

Paulseu et al. (1996)

Rumsey et al. (1997)

Horwitz et al. (1998)

Shaywitz et al. (1998)

Brunswick et al. (1999)

Paulesu et al. (2001)

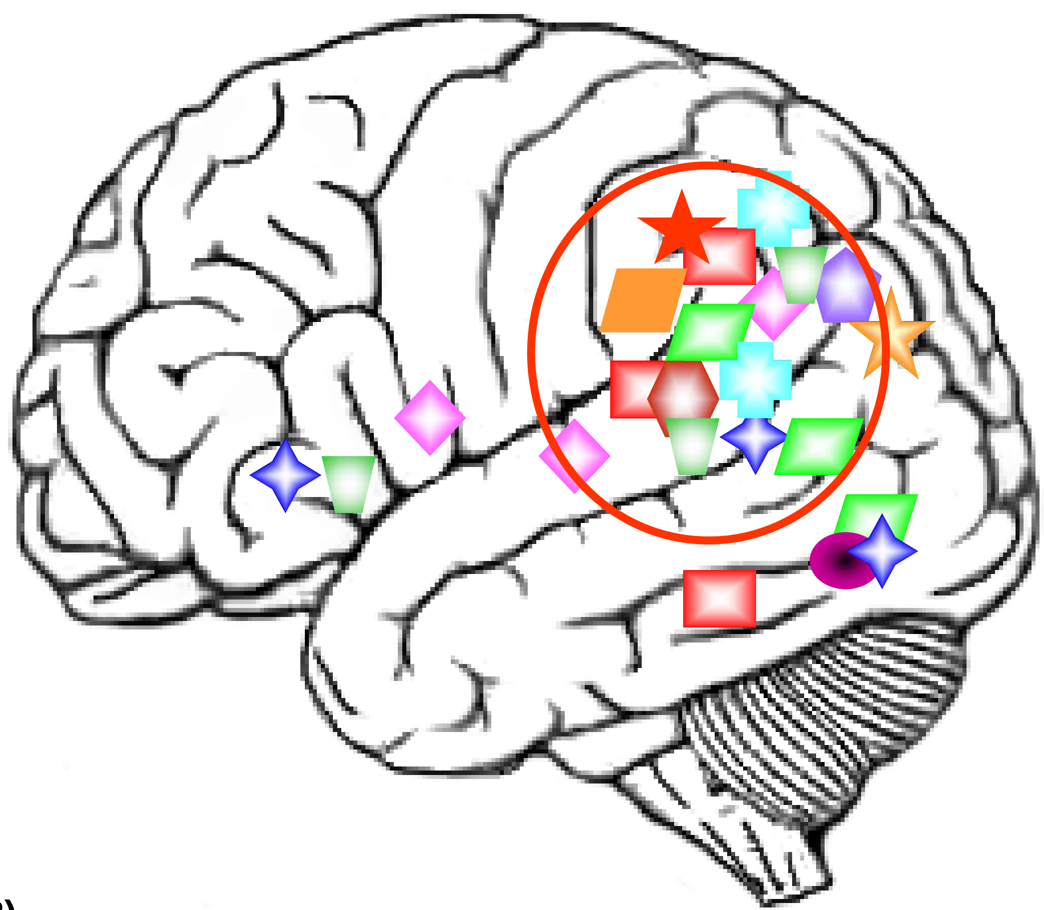
Temple et al. (2001)

Shaywitz et al. (2002)

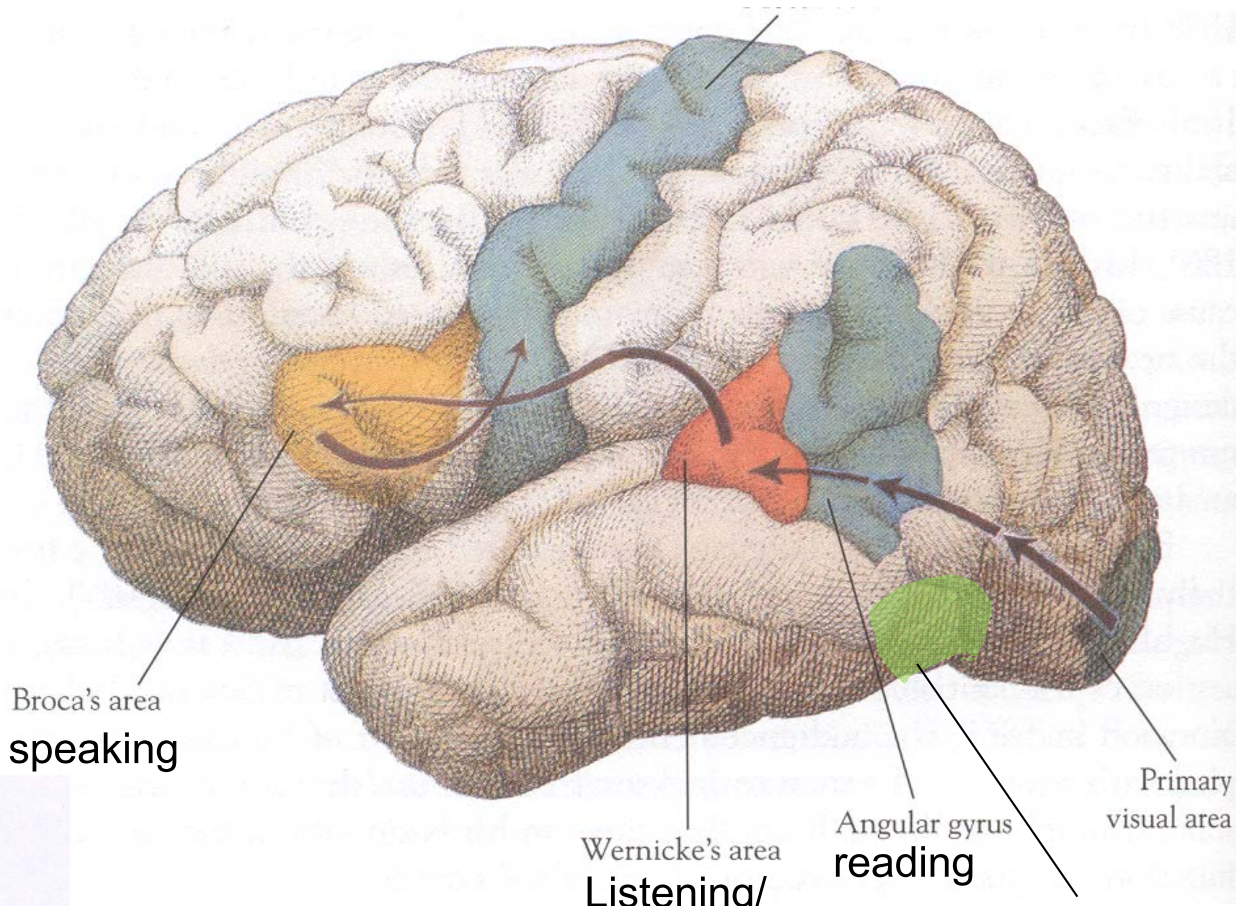
Eden et al. (2004)

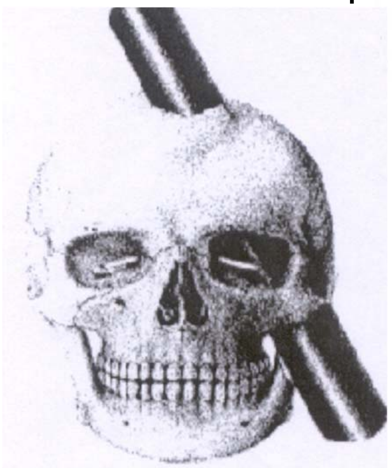
Hoeft et al. (2007)

Many new studies (2007-2013)



Brain systems involved in speaking and reading

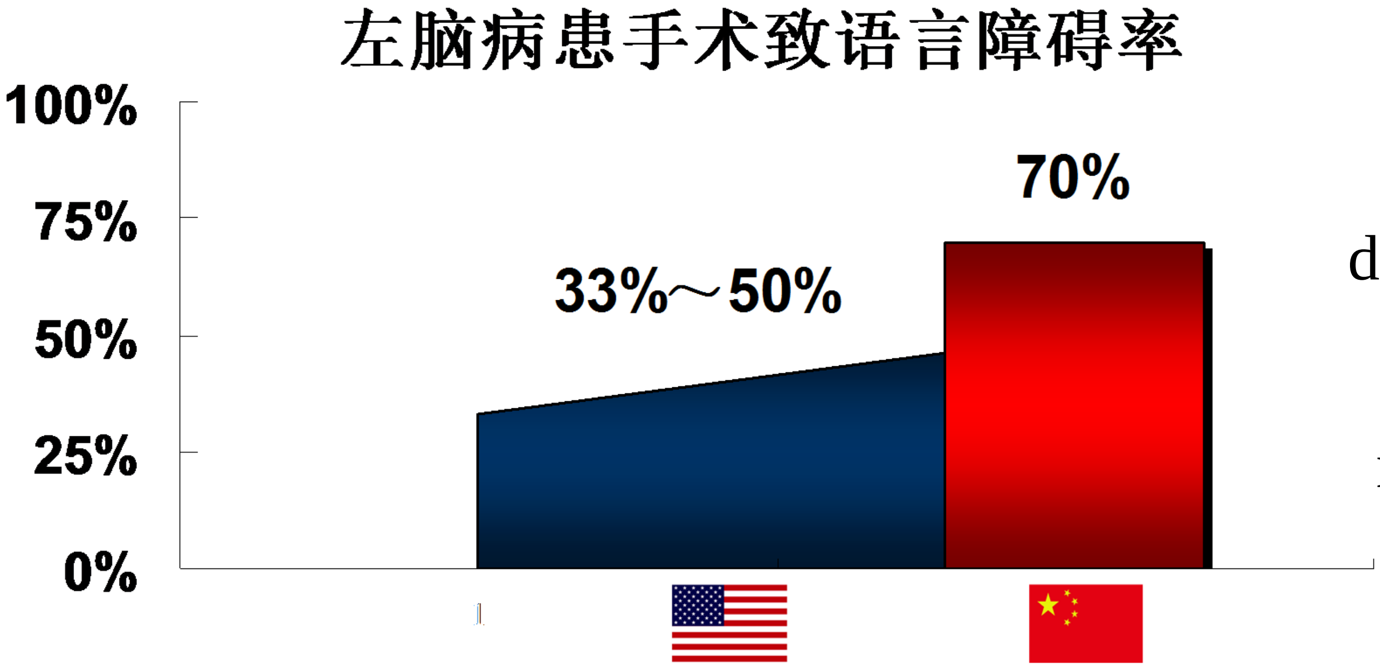




Are there language-specific brain regions?

Suggestive evidence from brain diseases
affecting language functions: epilepsy, tumor, stroke, brain palsy…

➢Neurosurgery
9M patients of epilepsy, 20% with surgery

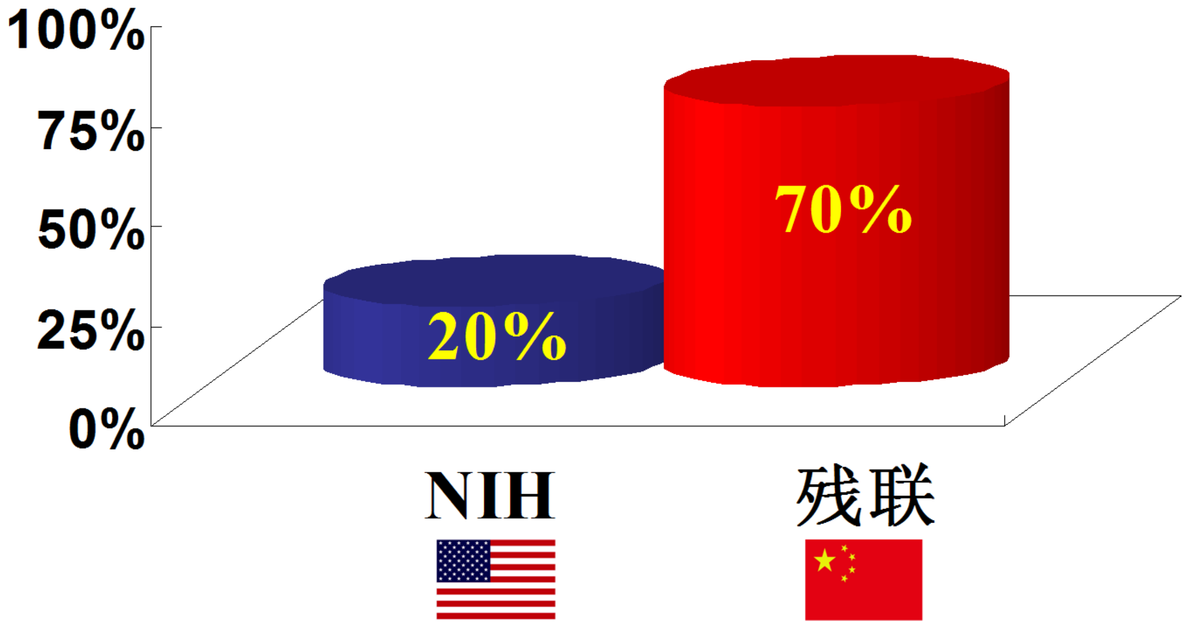


• % of patients with left hemisphere damages suffering language disorders after neurosurgeries in USA & China

600萬中國腦癱患者和200萬美國腦癱患者語言障礙發生率

% of brain palsy patients with severe language disorders in USA and China

脑瘫患者语言障碍发病率



These data indicate, language disorders caused by brain diseases are more severe in China

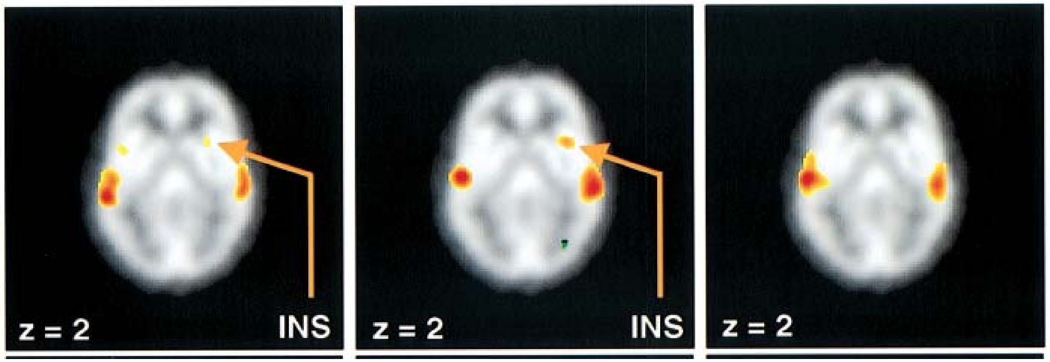
Why? Do language differences matter?

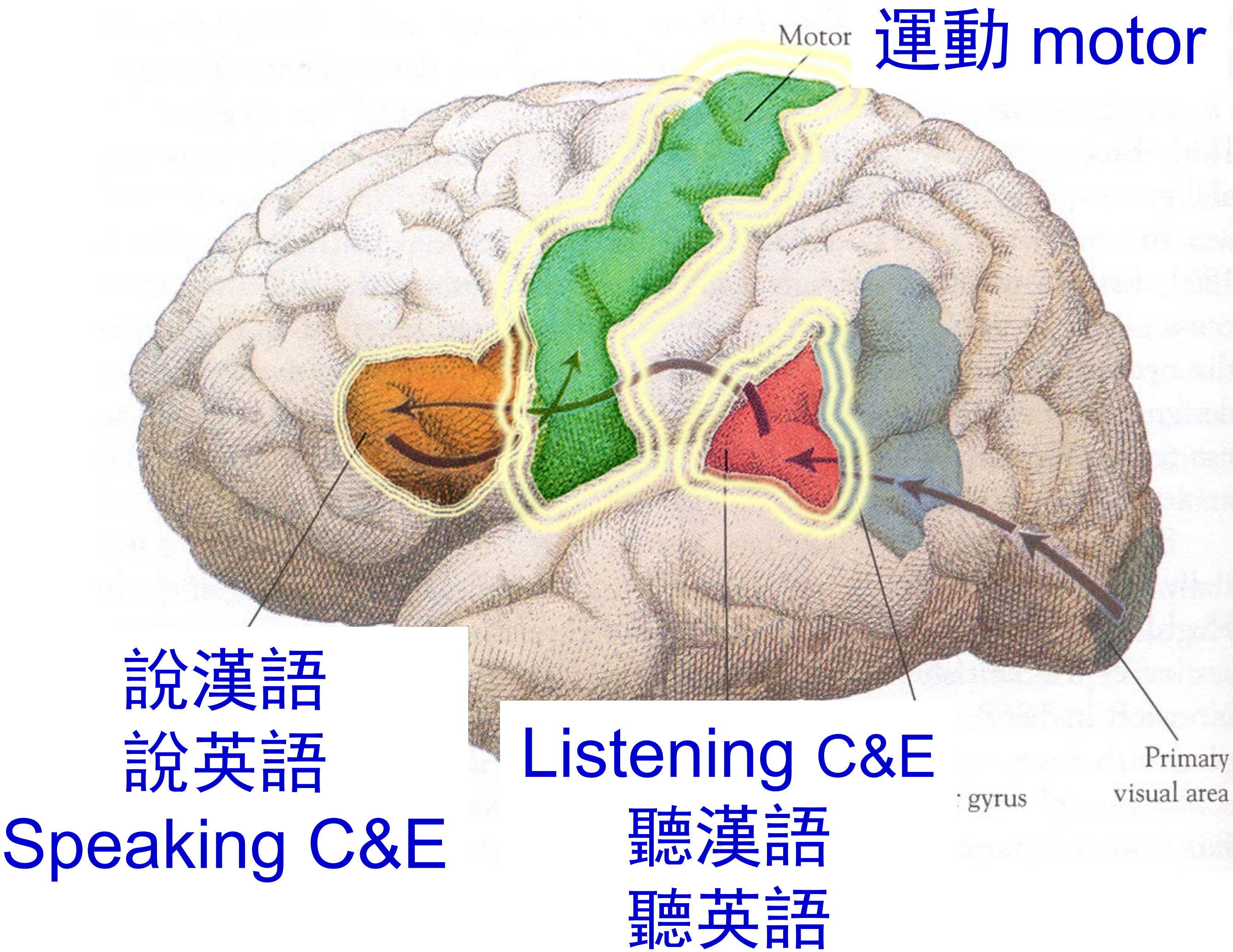
大腦負責中國語言聽和說的中樞
Brain regions for listening & speaking of the Chinese language

- 中國語言(在此指漢語和中文)與英語等西方語言有著顯著區別。

  口頭語言來說：帶調 與 非帶調

Chinese: tonal language
English: non-tonal language





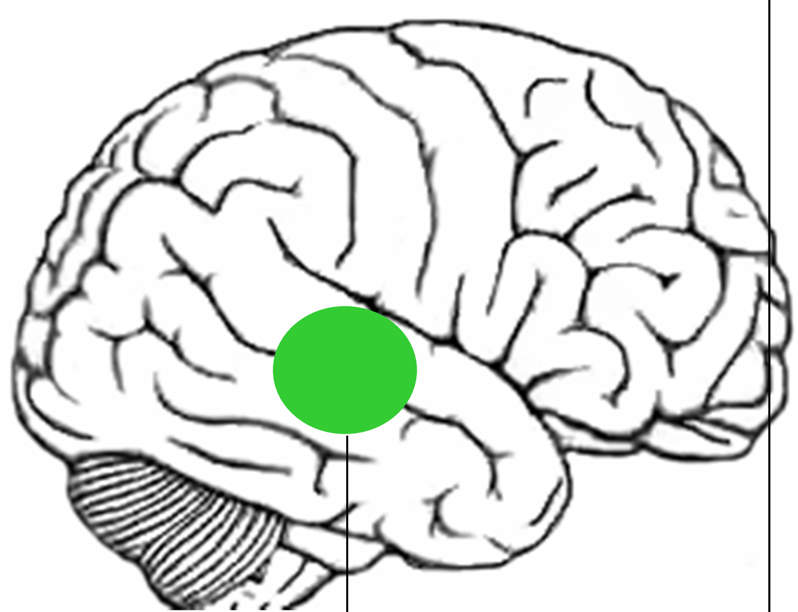
主管漢語和西方語言聽和說的腦區有部分重疊。

聽: 左顳葉

說: 左額下回

布羅卡區和韋爾尼克區主管漢語的聽和說的能力

(Gandour et al)



聽說漢語
Chinese: listening & speaking

大腦的漢語理解中樞: 不僅左腦額下回和顳葉主管口語加工(與西方語言相同), 右腦顳上回對漢語聲調加工也有獨特作用。

Right superior temporal cortex crucial for Chinese tone processing

Gandour et al. (NeuroReport, 1999? NeuroImage, 2004;

Peng et al., (NeuroImage, 2006)

Luo et al. (PNAS, 2006)

Chinese Reading Ability and Disability

Written Chinese 中文: 表意文字 (Wang, 1973) (logographic system)

国 網

- **Visual Form:**
  holistic vs. linear

- **Sound 字音:**

Characters > <u>syllables</u>:
addressed phonology

English words > <u>phonemes</u>:
assembled phonology

Cortical Regions for Chinese Reading

Word generation 蓝 >天
(blue > sky)

Rhyme decision 歌 + 颗
(ge > ke)

Homophone decision 谢 + 泻
(xie > xie)

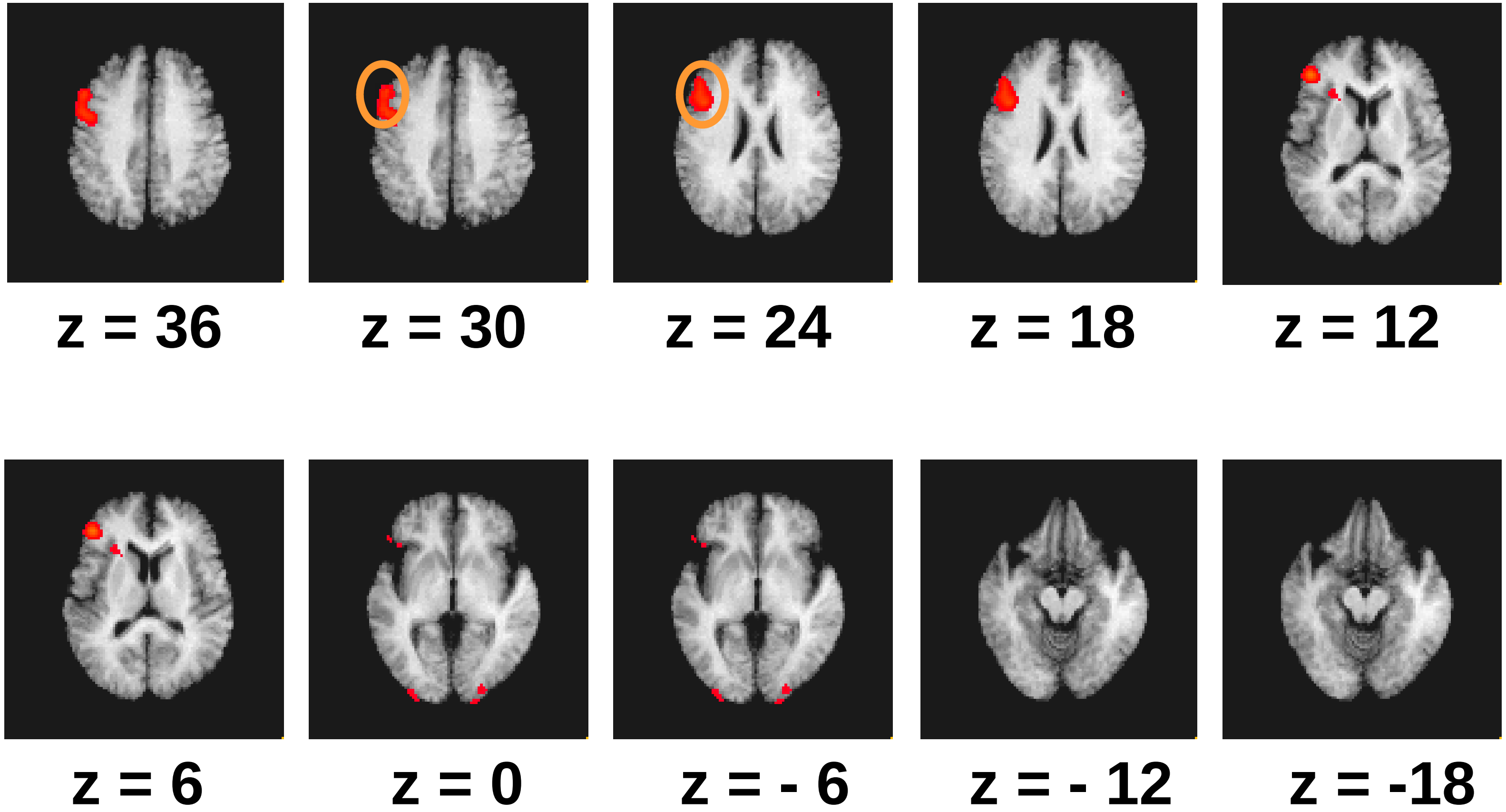
Semantic decision 妈 + 母
(ma > mu)

………………

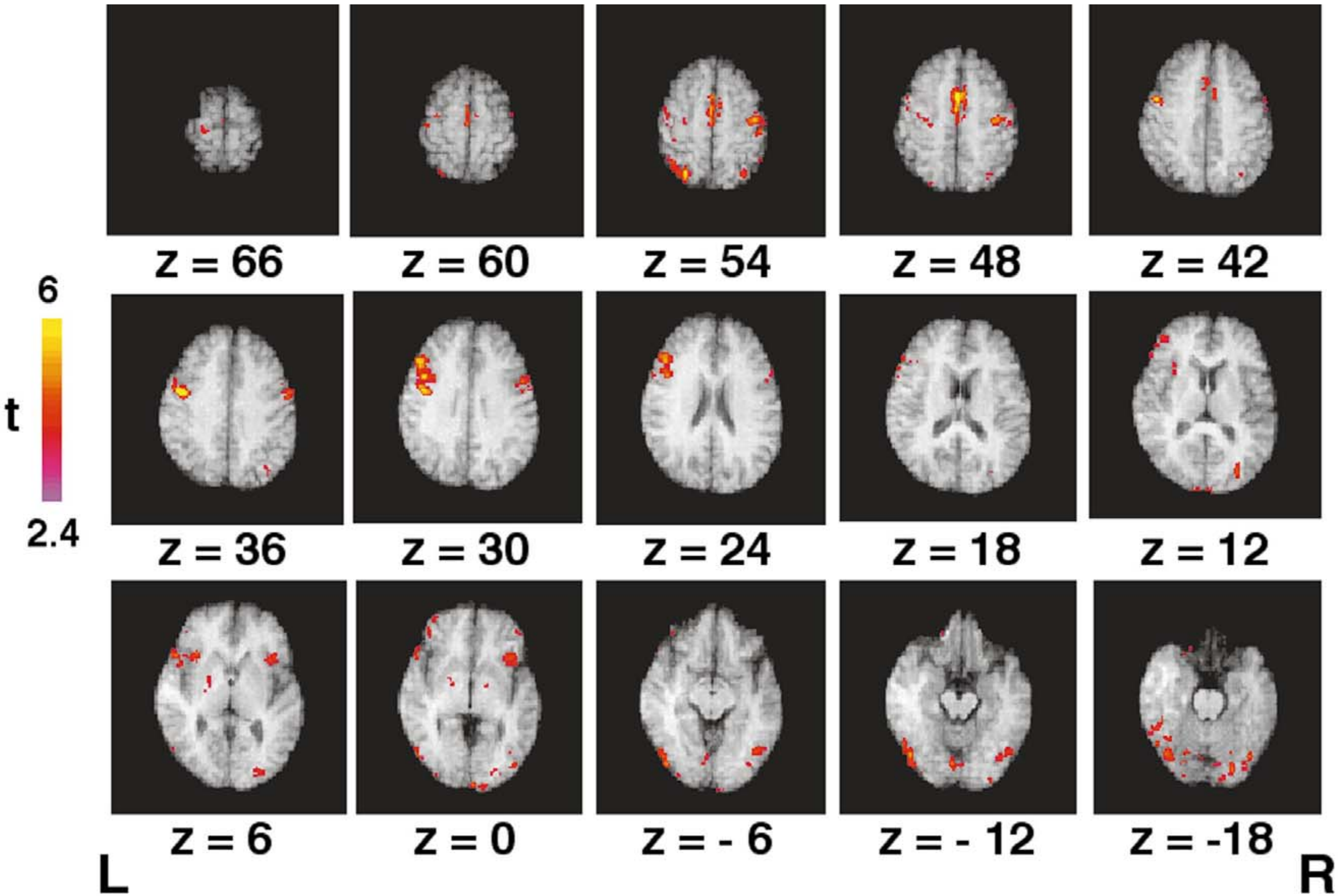
Hum Brain Mapp, 2000;
NeuroImage, 2001;
NeuroReport, 2001;
Hum Brain Mapp, 2003;
Nature,2004;
PNAS,2005;
Hum Brain Mapp, 2005;
PNAS, 2008;
Annals of NYAS, 2008;
Current Biology, 2009;
PNAS, 2011;
PNAS, 2012
………

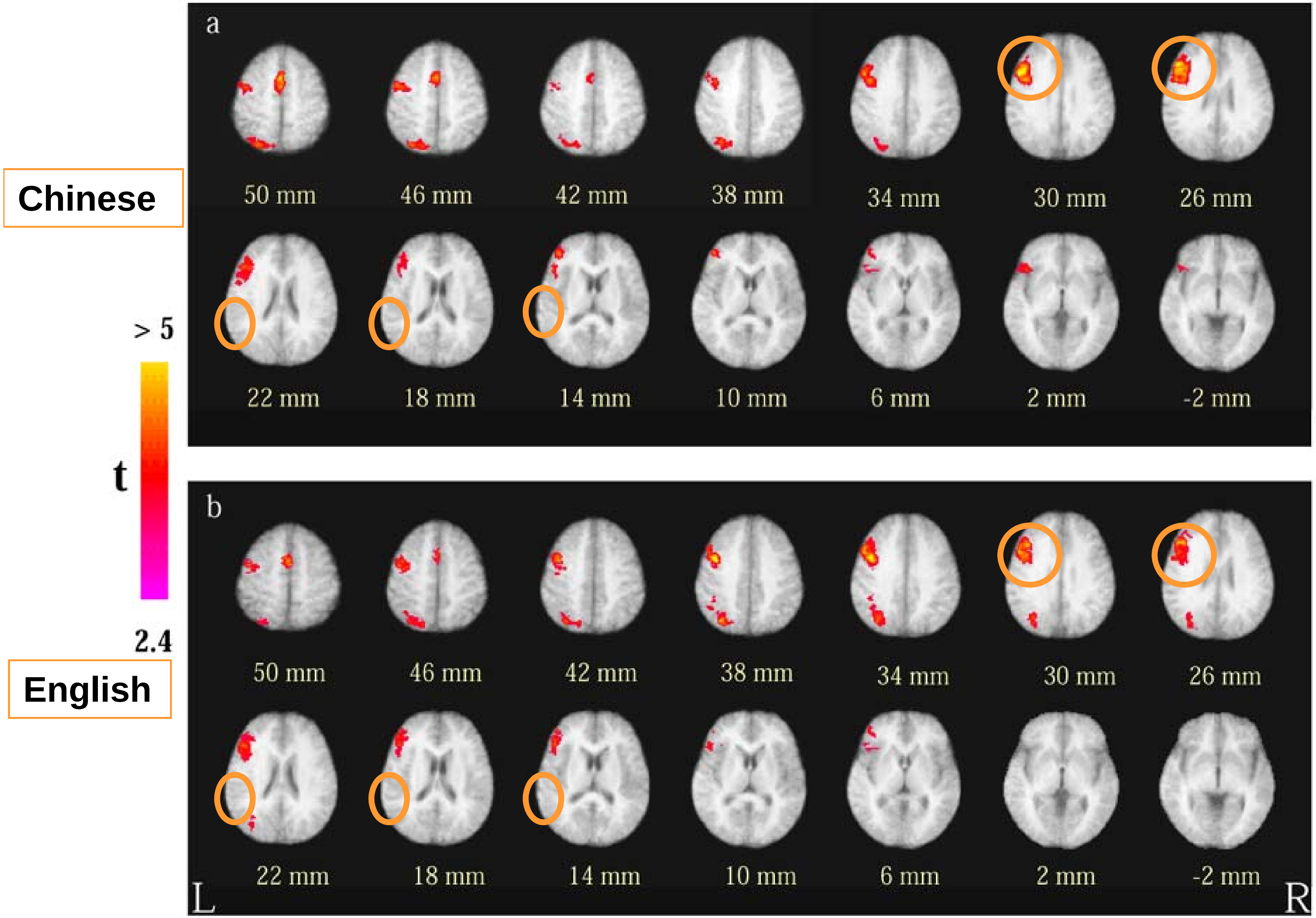
Left middle frontal region is critical for Chinese reading

左額中回



Left middle frontal region and bilateral fusiform gyri





Chinese
English
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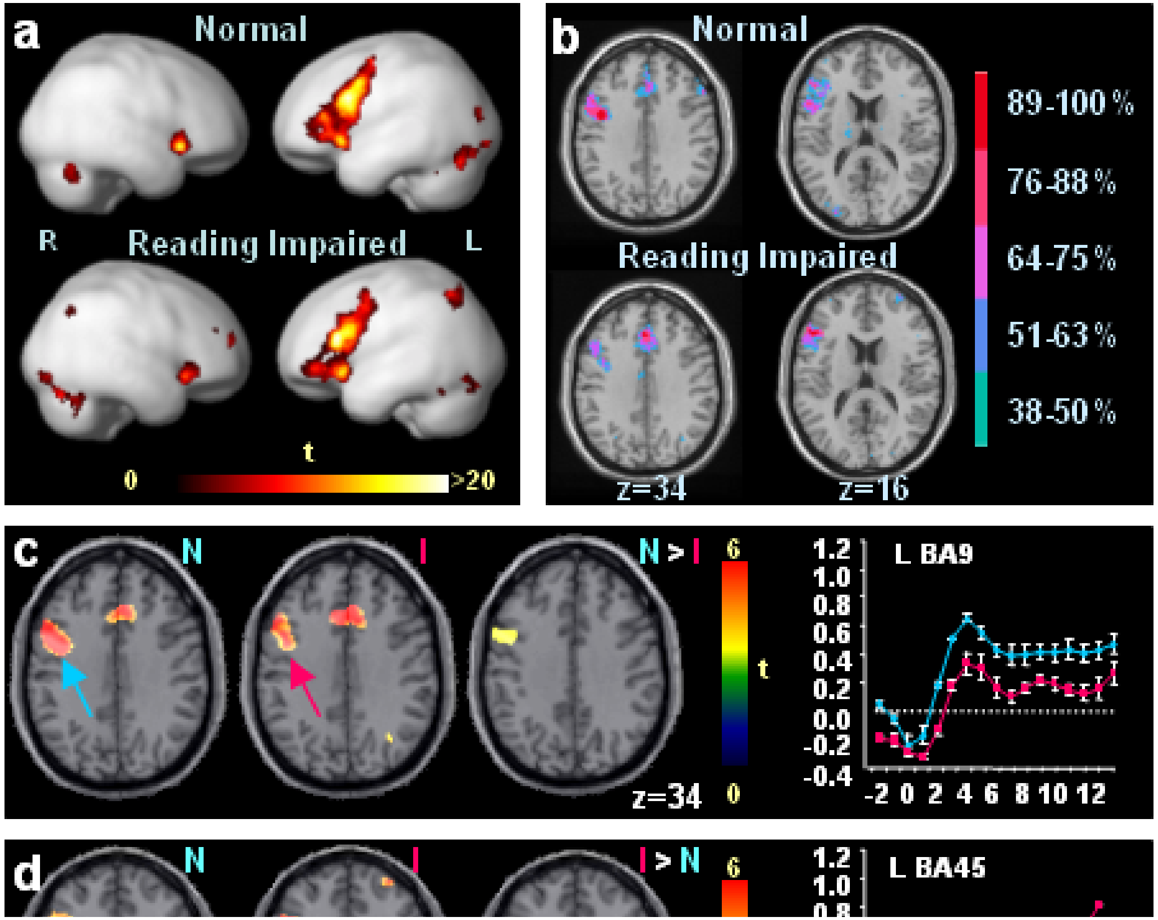
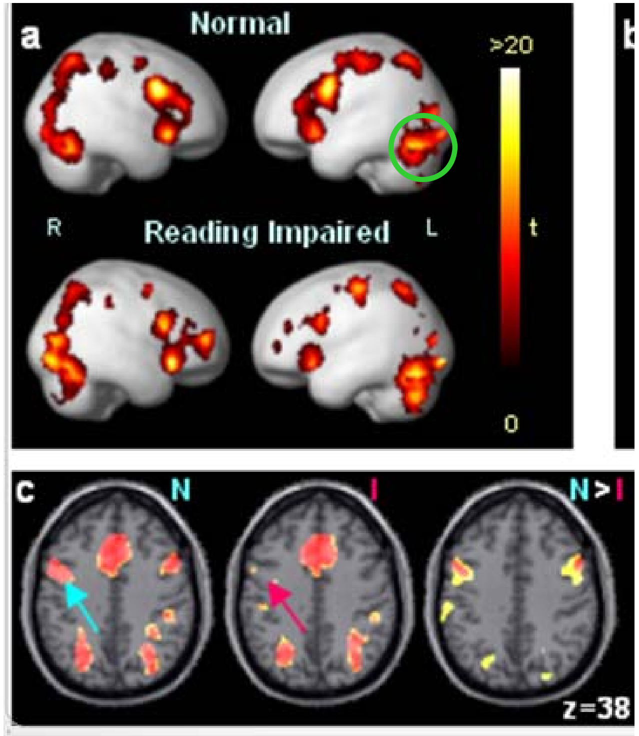
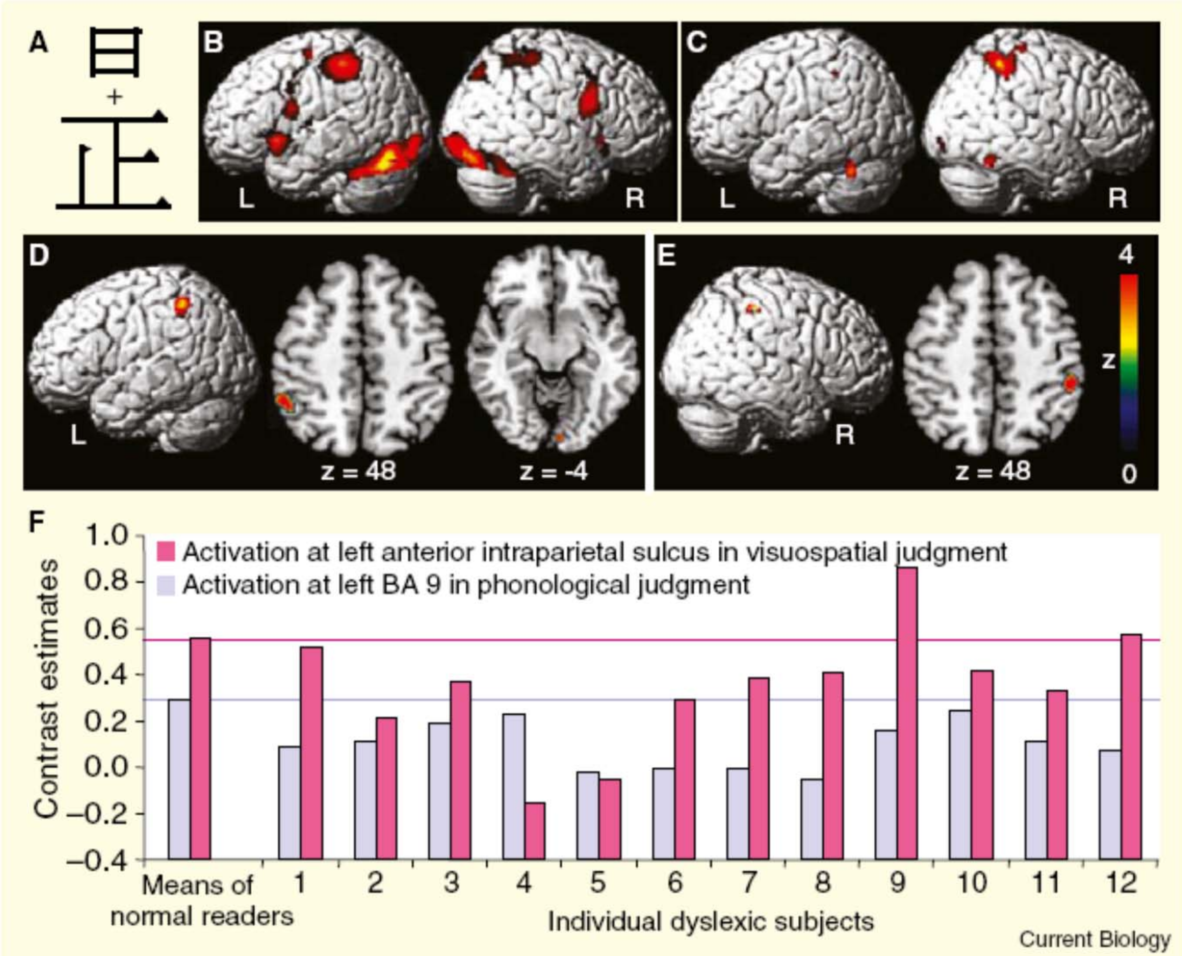




Impaired reading shows weaker neural activity than normal readers at left middle frontal gyrus and a few other regions but the right occipital cortex has a reversed pattern.



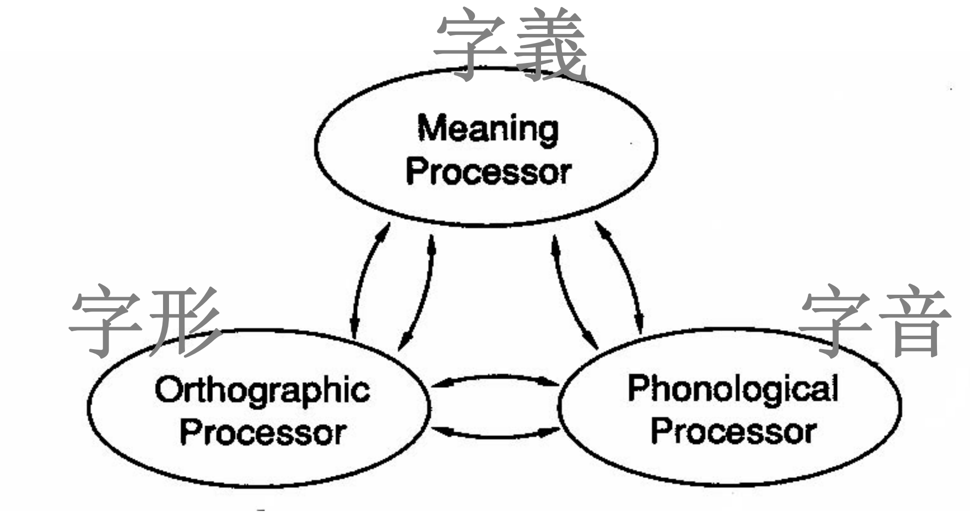
Results from the physical size decision:

Left intraparietal sulcus mediates visuospatial processing of Chinese characters

1. Dyslexics show weaker activations in left intraparietal sulcus (IPS) mediating visuospatial processing.

2. Individual variability analysis shows that visuospatial & phonological deficits co-exist in the majority (83.33%) of Chinese dyslexics.

Possible role of left middle frontal gyrus in reading Chinese 左額中回的作用



Coordination of cognitive resources and **memory**:

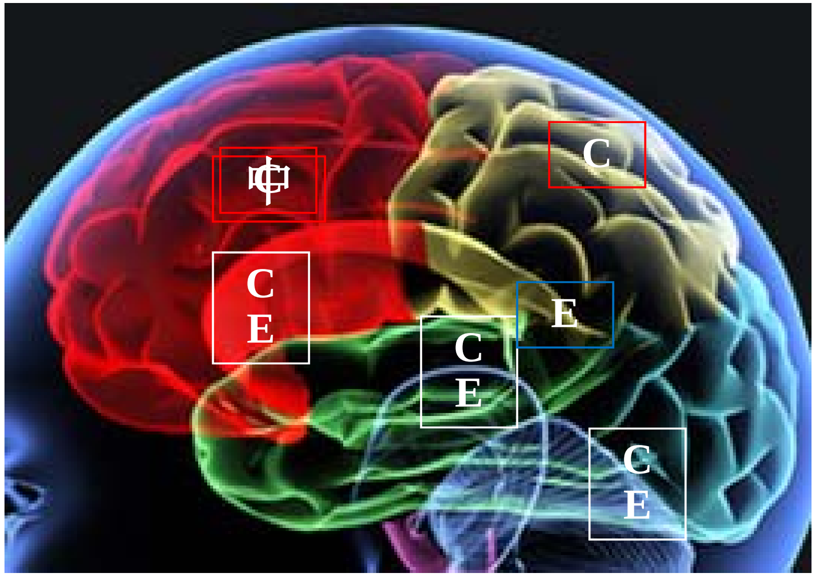
orthography-to-phonology mapping

orthography-to-semantics mapping

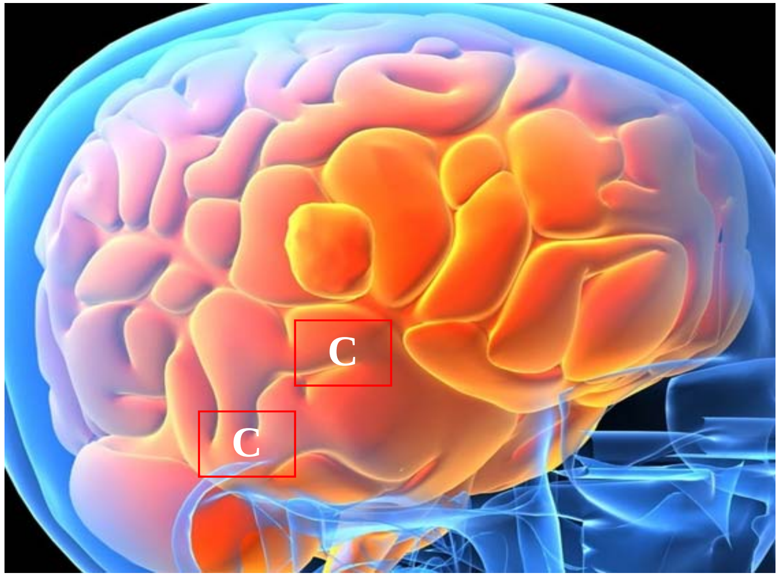
Brain systems of language

(including speaking, listening, and reading)

L



R



C = Chinese; E = English

The culture-specific theory

Written Chinese as a logographic language is cognitively and neuro-anatomically represented differently in some important aspects in comparison to alphabetic languages.

Exp Brain Res (2008) 184:427–433
DOI 10.1007/s00221-007-1200-0

RESEARCH NOTE

Optical imaging of phonological processing in two distinct orthographies

Hsin-Chin Chen · Jyotsna Vaid · Heather Bortfeld · David A. Boas

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D. A. Boas
Anthinoula A. Martinos Center for Biomedical Imaging,
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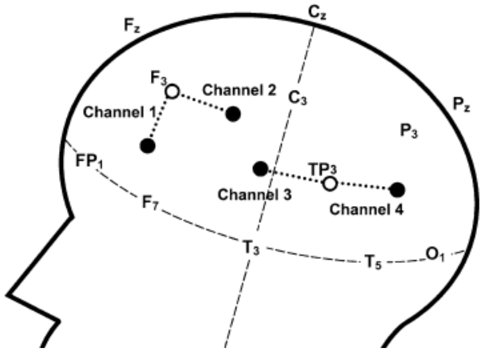
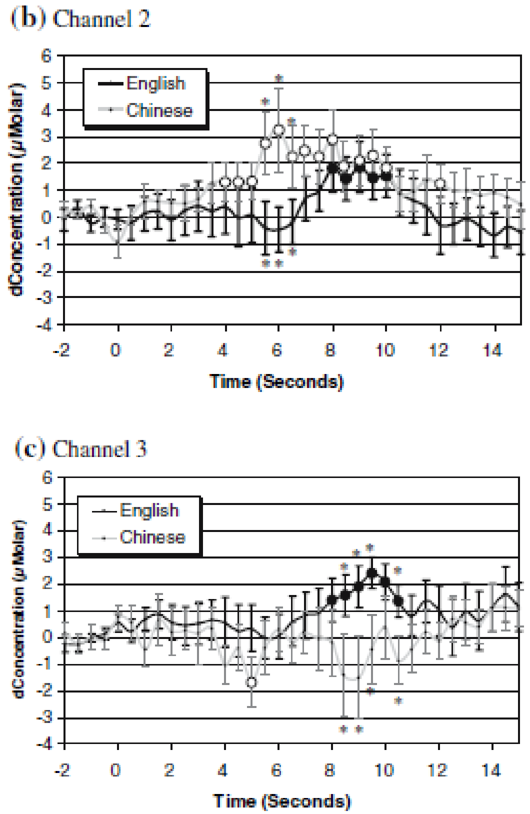




"…the present results suggest an important role of the left middle frontal gyrus (BA9) for Chinese character processing and a special role of the left superior temporal gyrus (BA22) and supramarginal gyrus (BA40) for English readers."

NEUROCASE
2012, *iFirst*, 1–8

Psychology Press
Taylor & Francis Group

A near-infrared brain function study of Chinese dyslexic children

Ranran Song[1], Jiajia Zhang[2], Bo Wang[1], Hui Zhang[1], and Hanrong Wu[1]

[1]Department of Child and Woman Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China
[2]Department of Epidemiology & Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA

Analysis of three kinds of blood hemoglobin in two groups for different channels

	Estimate	*Error*	*p-Value*
Total-Hb			
Group	−0.15	0.07	.037
Group*channel 1	−0.24	0.11	.026*
Group*channel 3	−0.28	0.11	.009**
Group*channel 11	−0.25	0.11	.020*
Oxy-Hb			
Group	−0.14	0.07	.0496
Group*channel 1	−0.00	0.10	.995
Group*channel 3	−0.27	0.11	.011*
Group*channel 11	−0.26	0.10	.010*
Deoxy-Hb			
Group	0.01	0.06	.826
Group*channel 1	−0.24	0.09	.009*
Group*channel 3	−0.17	0.09	.068
Group*channel 11	−0.14	0.09	.102

*$p < .05$, **$p < .01$.

DISCUSSION

In this study, we applied NIRS to detect the prefrontal cortex of dyslexia in Chinese language for understanding their poor reading ability. We designed the phonological detection and exchange tasks, allowing us to make a close comparison between the present findings using NIRS with those from other recent fMRI studies by Siok et al. (2004, 2008).

Our present study has demonstrated different cerebral blood patterns between dyslexic children and controls. And dyslexic children exhibited lower activity than controls in the left dorsolateral prefrontal cortex (DLPFC), which have been thought to be the core areas involved in processing. Firstly, during the phonological tasks, we observed an increase in oxy-Hb and total-Hb of the controls' prefrontal lobes, while there was a decreasing trend of these two parameters in dyslexic

doi:10.1093/brain/awq106 Brain 2010: 133; 1694–1706 | 1694

BRAIN
A JOURNAL OF NEUROLOGY

Developmental dyslexia in Chinese and English populations: dissociating the effect of dyslexia from language differences

Wei Hu,[1,2] Hwee Ling Lee,[3] Qiang Zhang,[1,2] Tao Liu,[1,2] Li Bo Geng,[1,2] Mohamed L. Seghier,[4] Clare Shakeshaft,[5] Tae Twomey,[6] David W. Green,[6] Yi Ming Yang[1,2] and Cathy J. Price[4]

1 Institute of Linguistics, Xuzhou Normal University, Xuzhou, Jiangsu Province, 221009, China
2 Jiangsu Key Laboratory of Language and Cognitive Neuroscience, Xuzhou, Jiangsu Province, 221009, China
3 Max-Planck Institute for Biological Cybernetics, 72076 Tubingen, Germany
4 Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London, WC1N 3BG, UK
5 The National Perinatal Epidemiology Unit, University of Oxford, Oxford, OX3 7LF, UK
6 Division of Psychology and Languages Sciences, UCL, London, WC1H OAP, UK

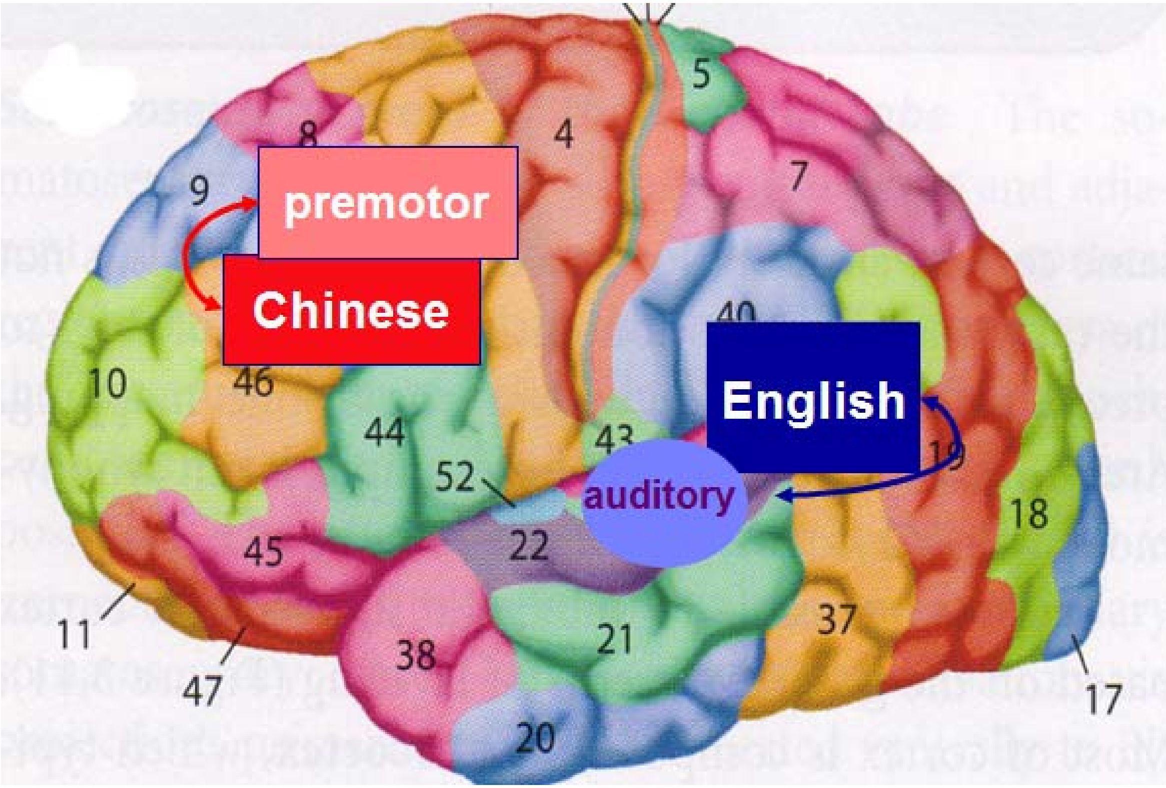
Chinese versus English normal readers

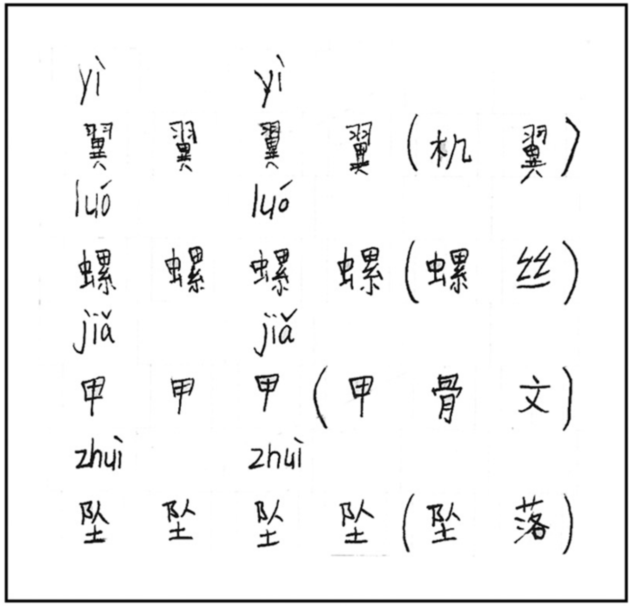
The activation patterns for semantic word matching were remarkably similar for Chinese and English monolingual normal readers (Supplementary Fig. 2), as observed in studies of Chinese–English bilinguals (Chee *et al.*, 1999). Nevertheless, a direct comparison of activation for semantic word matching in Chinese and English monolingual readers also demonstrated differences that were consistent with studies of Chinese–English bilinguals (Tan *et al.*, 2001, 2003). Specifically, we found that semantic word matching activation was greater in Chinese than English readers in the LIFS on the boundary between the left middle and inferior frontal gyri with peak co-ordinates in Montreal Neurological Institute space at $x = -46$, $y = +6$, $z = +30$, a Z-score of 3.4 and 20 voxels at $P < 0.001$. The peak co-ordinates are in close proximity to those that Tan *et al.* (2001) first identified with Chinese reading ($x = -45$, $y = +13$, $z = +30$) and our effect was highly significant following small volume correction for multiple comparisons ($P < 0.02$ corrected) based on Tan *et al.*'s previous result. In contrast, English readers had greater activation than Chinese readers in the LpSTS. The peak co-ordinates ($x = -56$, $y = -38$, $z = +6$) for this effect were also within the area (from $x = -57$, $y = -42$, $z = +21$ down to $z = +6$) that Tan *et al.* (2003) reported when English monolinguals read English but not when Chinese–English bilinguals read English.

Chinese versus English dyslexic readers

Why the left middle frontal gyrus plays an important role in Chinese reading?

Why the left posterior temporoparietal regions are crucial for English reading?



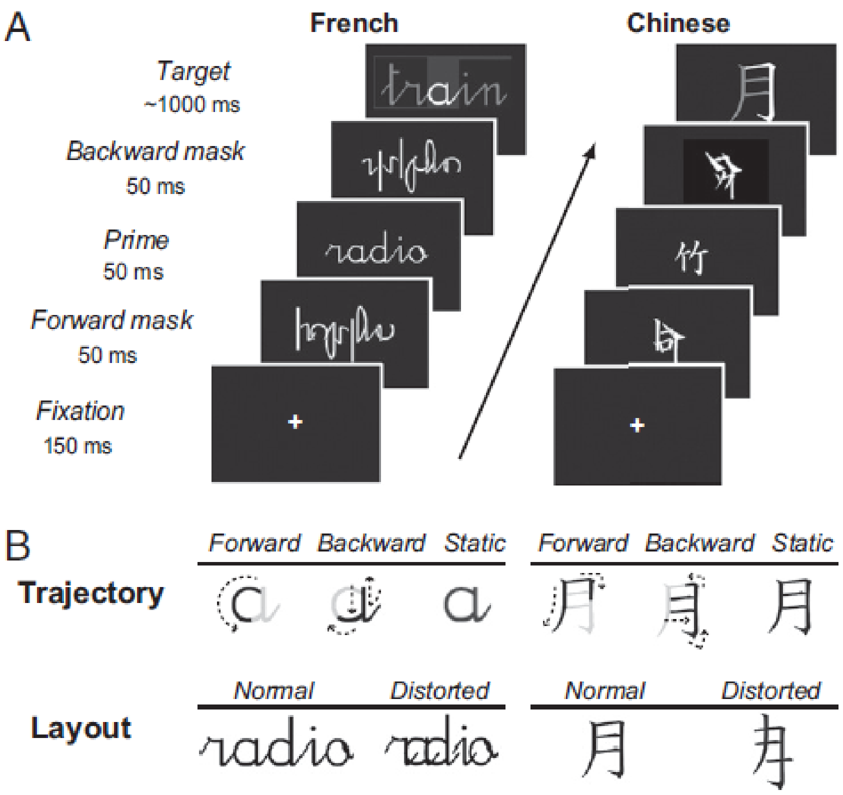


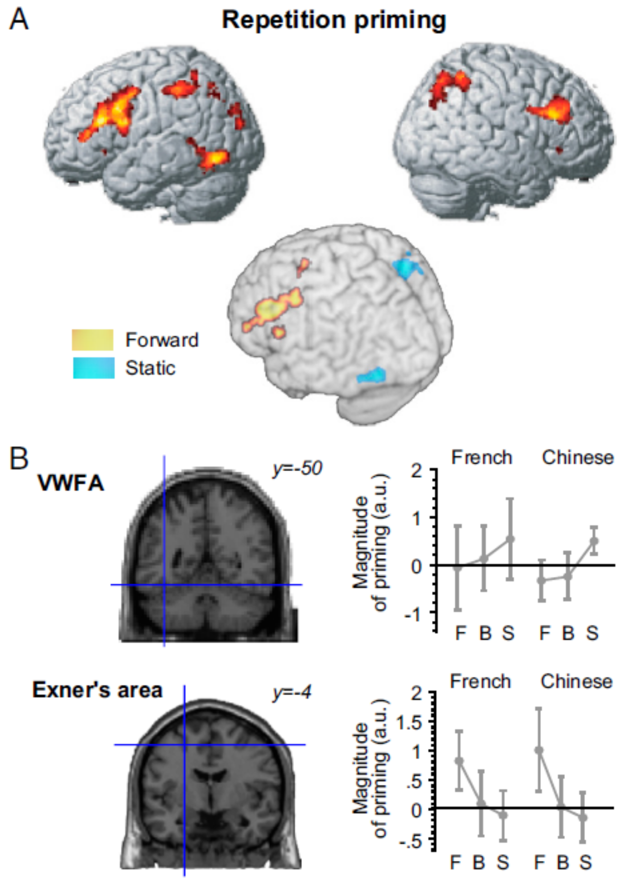
Children are asked to repeatedly copy characters as homework;
effects of learning experience

Universal brain systems for recognizing word shapes and handwriting gestures during reading

Kimihiro Nakamura[a,b,c,d], Wen-Jui Kuo[e], Felipe Pegado[a,b,c,d], Laurent Cohen[f,g,h], Ovid J. L. Tzeng[i,j], and Stanislas Dehaene[a,b,c,d,1]

[a]Cognitive Neuroimaging Unit, Institut National de la Santé et de la Recherche Médicale (INSERM), F91191 Gif-sur-Yvette, France; [b]NeuroSpin Center, Commissariat à l'Energie Atomique (CEA), Institut Fédératif de Recherche (IFR) 49, F91191 Gif-sur-Yvette, France; [c]Université Paris XI, 91405 Orsay, France; [d]Collège de France, 75231 Paris, France; [e]National Yang-Ming University, Taipei 11221, Taiwan; [f]Faculté de Médecine Pitié-Salpêtrière, Université Paris VI, 75651 Paris, France; [g]Department of Neurology, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique–Hôpitaux de Paris (AP-HP), 75651 Paris, France; [h]Institut du Cerveau et de la Moelle épinière (ICM) Research Center, INSERM, Unité Mixte de Recherche Sciences 975, 75651 Paris, France; [i]Academia Sinica, Taipei 11574, Taiwan; and [j]Brain Research Center, National Chiao Tung University, Hsinchu, Taipei 30010, Taiwan





What happens if a Chinese child does not spend much time on handwriting/copying?

For example, nowadays so many children use the Pinyin input method when texting.

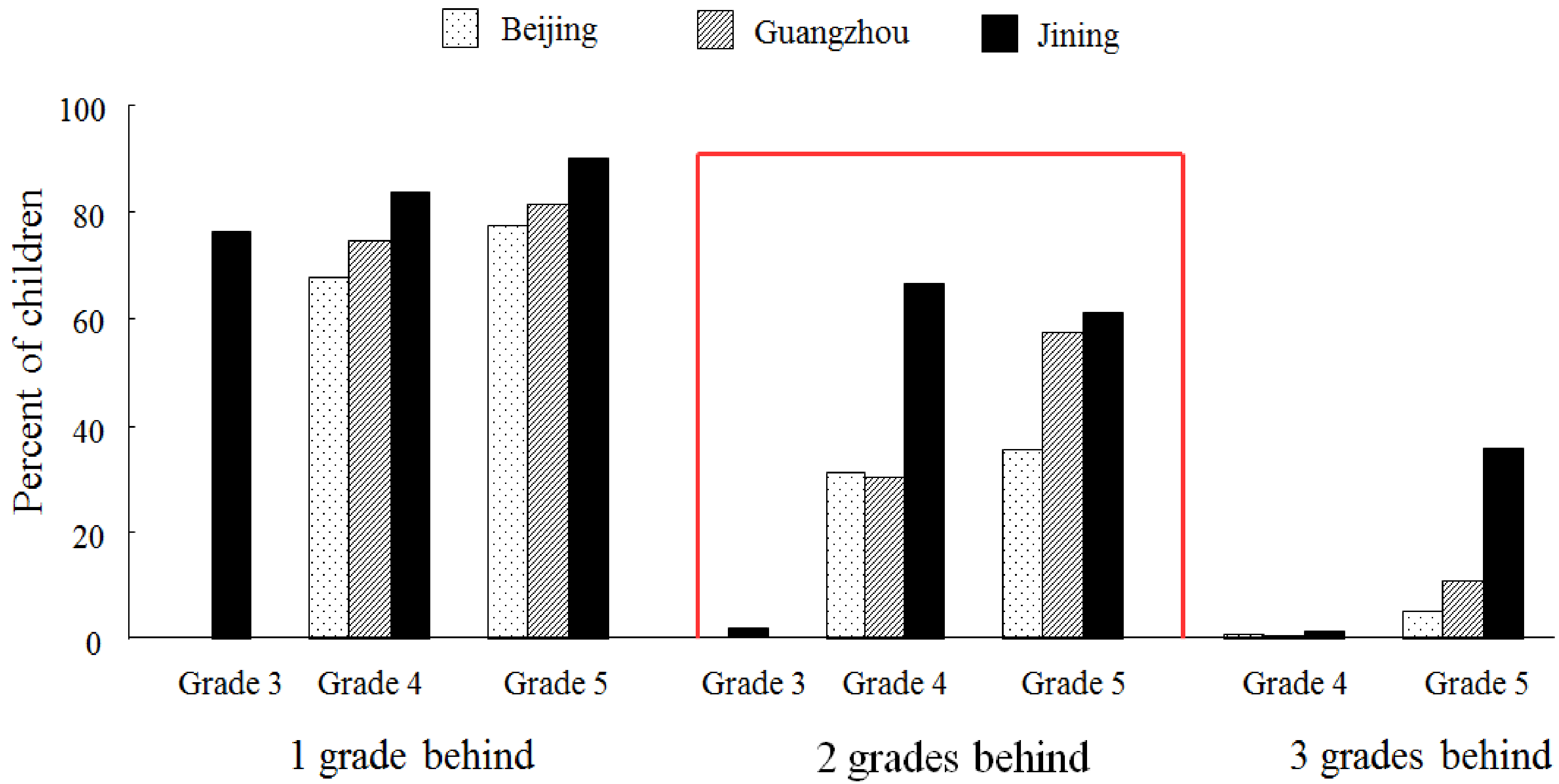
China's language input system in the digital age affects children's reading development

Li Hai Tan[1,2], Min Xu[1], Chun Qi Chang, and Wai Ting Siok[2]

State Key Laboratory of Brain and Cognitive Sciences, Department of Linguistics, and Shenzhen Institute of Research and Innovation, University of Hong Kong, Hong Kong

Edited by Dale Purves, Duke–National University of Singapore Graduate Medical School, Singapore, and approved December 5, 2012 (received for review August 7, 2012)

	Beijing		Guangzhou		Jining		
	Grade 4	Grade 5	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
No. of children	263	203	250	227	1,262	1,322	2,324
No. of boys	146	109	145	114	669	714	1,288
No. of girls	117	94	105	113	593	608	1,036
Mean age in months (SD)	114.55 (4.58)	126.90 (5.50)	121.71 (4.22)	134.21 (4.72)	110.18 (5.38)	121.80 (6.14)	133.83 (5.08)
No. of children administered the nonverbal IQ test	262	203	248	226	1,222	1,247	1,209*
Mean nonverbal IQ in percentile (SD)	75.02 (21.16)	73.08 (23.52)	67.94 (25.15)	70.71 (24.66)	72.31 (24.51)	68.64 (23.78)	70.45 (24.40)
No. of missing data (date of birth, reading score)	—	—	2	1	21	44	4



- Significant and positive correlations between reading performance and handwriting: $r = 0.29$ and $P < .0001$ for third graders, $r = 0.34$ and $P < .0000$ for fourth graders, and $r = 0.45$ and $P < .00000$ for fifth graders.
- Children's reading scores were negatively correlated with the use of the pinyin input method, with a stronger correlation found at the higher grade: $r = -0.347$ and $P < .00000$ for fourth graders, and $r = -0.405$ and $P < .000000$ for fifth graders.
- No significant correlation between pinyin typing time and handwriting time ($r = -0.015$ for grade 4, and $r = -0.13$ for grade 5).
- Thus, Pinyin use has its own negative impact on reading, presumably because it interferes with the learning of the visuospatial properties of characters.

Is there a genetic basis for Chinese reading disorders?

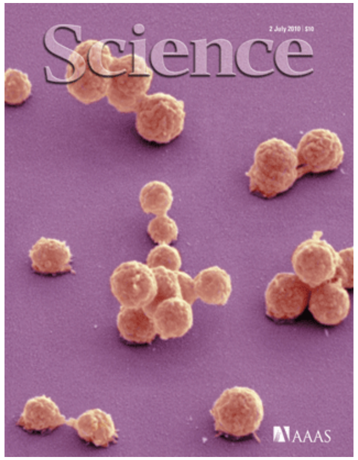
Genome-wide Association Study Of Developmental Dyslexia in Chinese Population

Yimin Sun, Yongyong Shi, Li-Hai Tan

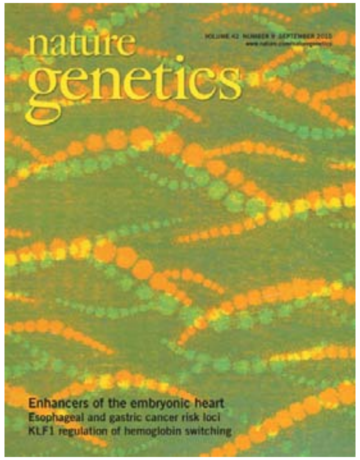
Tsinghua University
CapitalBio Corporation
Shanghai Jiaotong University
University of Hong Kong

GWAS Papers Supported by CapitalBio

Osteoporosis
2008, 83(6):663-674



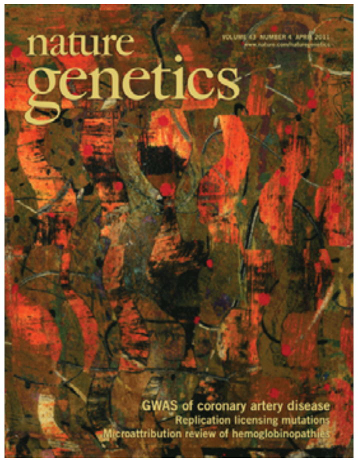
High-altitude adaptation
2010, 329(5987):72-5



Liver Cancer
2010, 42(9):755-8

Esophageal Cancer
2011, 43(7):679-84

Lung Cancer
2011, 43(8):792-796



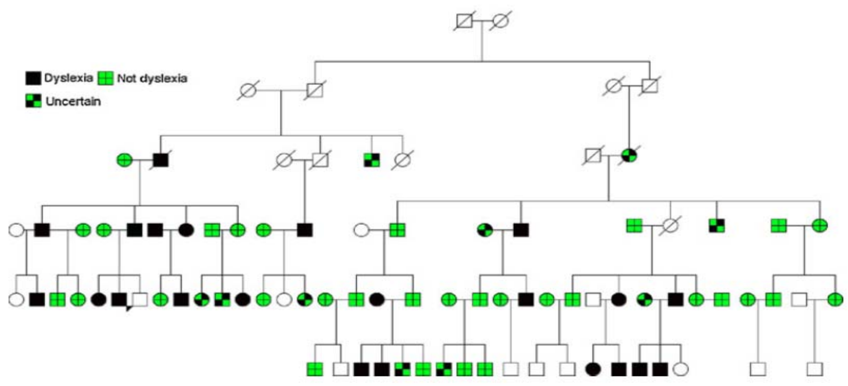
Coronary Artery Diseases
2011, 43(4):345-9

Pancreatic Cancer
2012, 44(1):62-66

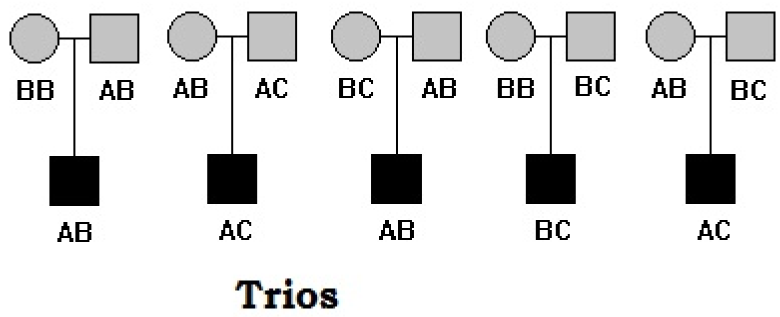
Non-obstructive Azoospermia
2012, 44(2):183-186

Genetic Study Strategies

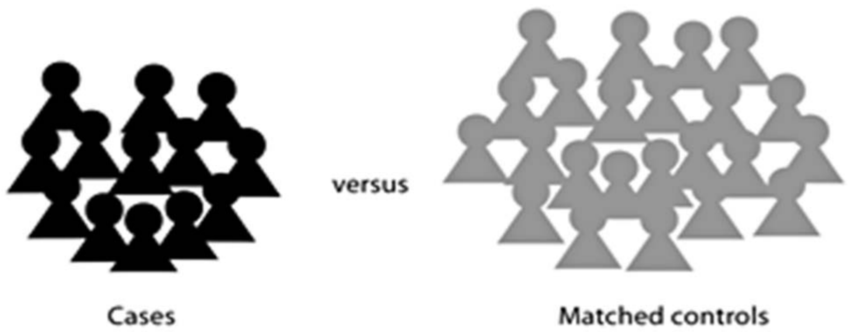
A: Linkage analysis based on extended families



B: Association/linkage study based on core families



C: Association study based case-control strategy



Nine DD Susceptibility Regions

Table 3 A summary of the *DYX#* loci

DYX#	Chromosome region	MIM	No. of positive studies[a]	References of positive studies[a]	No. of negative studies	References of negative studies	Candidate DD susceptibility genes
DYX1	15q21	127700	6	[29, 60, 72, 116, 124, 130, 157, 161, 174]	10	[10, 39, 47, 54, 94, 117, 127, 129, 144, 153]	*DYX1C1*
DYX2	6p22.3-p21.3	600202	7	[25, 26, 54, 55, 65, 71–73, 95, 117, 174, 193]	9	[29, 39, 46–48, 51, 93, 94, 127, 129, 130, 140, 146, 153, 157]	*DCDC2* and *KIAA0319*
DYX3	2p16-p15	604254	4 (+1)	[46–48, 54, 57, 117, 139] (+[94, 141])	4	[29, 39, 93, 127, 129, 146]	*MRPL19* and *C2ORF3*
DYX4	6q11.2-q12	[#127700]	1	[137]	8	[39, 47, 54, 93, 94, 117, 127, 129, 146]	–
DYX5	3p12-q13	606896	2 (+1)	[54, 78, 127] (+ [54, 117])	5	[39, 47, 93, 94, 129, 146]	*ROBO1*
DYX6	18p11.2	606616	3	[54, 117]	7	[29, 39, 47, 93, 94, 127, 129, 146, 160]	–
DYX7	11p15.5	[#127700]	1 (+1)	[90] (+ [54, 117])	7	[39, 47, 54, 93, 94, 127, 129, 146]	–
DYX8	1p36-p34	608995	3	[74, 144, 194]	9	[39, 46–48, 54, 93, 94, 117, 127, 129, 146, 153]	*KIAA0319L*
DYX9	Xq27.2-q28	300509	1 (+1)	[39] (+ [54])	5	[39, 54, 94, 127, 129]	–

[a] Positive studies, and their references, in brackets indicate linkages close to the DYX# loci

Eur Child Adolesc Psychiatry, 2010, 19:179–197

Four DD Susceptibility Genes

Method	Gene	Results	References
Linkage and association studies in families	—	Replicated linkage of dyslexia to chromosome 15	35, 62, 65, 80
Targeted sequencing and association analysis	*DYX1C1*	Identified two SNPs associated with dyslexia	96
Association study in families	*DYX1C1*	Found a nonsynonymous SNP associated with dyslexia	7
Linkage analysis in a family	—	Detected significant linkage to chromosome 3 in a Finnish family	71
Candidate gene sequencing	*ROBO1*	Found that partial haploinsufficiency for ROBO1 may cause dyslexia in humans	40
Linkage and association studies in families	—	Suggested chromosome 6p21 as a locus for dyslexia	28, 35, 36, 89, 98
Association studies in a candidate locus	*DCDC2* and *KIAA0319*	Suggested *DCDC2* and *KIAA0319* as candidate genes for dyslexia	13, 30, 41, 64, 81

Annu. Rev. Genomics Hum. Genet., 2011, 12:145–64

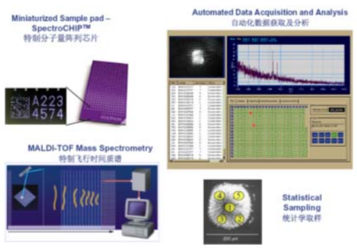
By now, there is no published genome-wide association study for developmental dyslexia

Three-stage GWAS Design

Stage I: Whole-genome SNP detection (millions of SNPs)


Affymetrix : CHB 1 & 2
1284887 SNPs

Stage II: Replication I (about fifty SNPs)

Sequenom

Stage III: Replication II (about twenty SNPs)



Sequenom/Taqman

30,368 Chinese children were tested to identify dyslexics/impaired readers

对我国30368名儿童进行了系统的语言和非语言能力测试，鉴定筛选出了1500余名阅读障碍患者（和3000余名阅读成绩优异的对照组儿童），建立了我国首个阅读障碍研究队列，为深入探讨影响儿童语言能力发展的环境、学习和基因等因素提供了可靠的样本保证。

项目组在山东济宁市、梁山县和东明县战斗约10个月

济宁市市中区

约14,000名小学生；其中9,000参加测试。山东教育出版社教材。

济宁市和平街小学
济宁市永丰街小学
济宁市明珠小学
济宁市普育小学
济宁市十二中小学部
济宁市霍家街小学

济宁市梁山县县城

共3所小学9,139名小学生，其中两所最大规模的小学7,140人全部参加测试。人教社教材。

梁山县第一实验小学
梁山县第二实验小学

菏泽市东明县县城

共6所小学13,968名小学生，全部参加测试。江苏教育出版社教材。

东明县第一实验小学
东明县第二实验小学
东明县第三实验小学
东明县明贤小学
东明县玉成小学
东明县南门小学

测试内容

■ 第一阶段：班级语文测验（30368名儿童全部参加）

根据班级语文测验结果，先排除掉一年级，然后从二年级以上各年级筛选出语文成绩最好的15%和最差的15%（济宁、梁山）或13%（东明），总计筛选出7214名。（济宁2400，梁山1788，东明3026）

■ 第二阶段：对7214名儿童进行标准化的个体阅读测试（5分钟）和集体非语言智力测验（45分钟，每40人1组）。每天平均测试6小时。10余名助手同时测试，约需要70天。

■ 第三阶段：筛选出阅读障碍患者和对照组，对梁山和东明约1500名阅障者和约3000名控制组儿童采集基因样本。10多名助手用了约20天采集完所有基因样本。 Saliva and buccal swabs were acquired for the DNA extraction

■ 第四阶段：对梁山的1055名儿童（阅障者和控制组）进行近10余项行为测试，采集了大量有关阅读障碍的行为学特征的数据。10几名助手每天测试6至7小时，总计测试27天。


仁爱和谐 主体发展

Stage I: Subjects

A total of **501** DD children **(391:110)** and **521** paired non-DD ones **(221:300)** were recruited with informed consent from about 7000 primary school students aging 8-12 years.

Saliva and buccal swabs were acquired for the DNA extraction.

- Chinese character reading;
- Raven's Standard Progressive Matrices;
- Chinese onset;
- Rapid naming;
- Visual form constancy;
- Visual-spatial relationship
- Component search;
- Character copy

……

Quality Control

Affymetrix GeneTitan

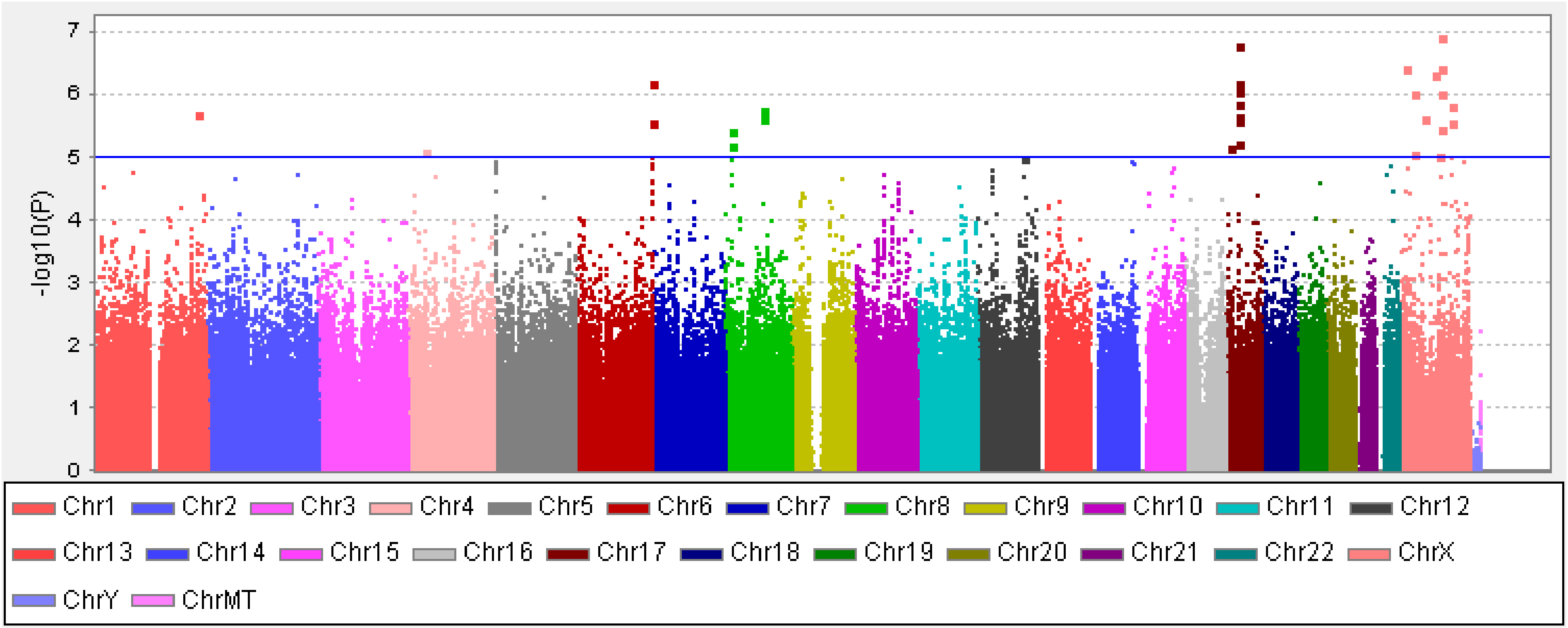
Category	CHB1	CHB1+2
Total Markers	640,673	1,296,521
Overlap with SNP 6.0	159,940	545,274
Overlap with 660W	139,511	229,407
Overlap with Omni Express	184,012	298,828

CHB: Chinese Han Beijing
(HapMap I, II, III+1000 genomes)

--40125 SNPs failed missingness test (GENO > 0.05)
--2 individuals removed for low genotyping (MIND > 0.05)
--8821 markers to be excluded based on HWE test (p <= 1e-005)
--57844 SNPs failed frequency test (MAF < 0.01)

After filtering: **498 cases, 516 controls, 1,183,484 SNPs**

Manhattan Plot



68 SNPs passed selection criteria for Chinese dyslexia in the discovery GWA scan. Manhattan plot of $-\log_{10}P$ values from the additive model after adjusting for age, sex and the first principal component.

Stage 2: Sequenom验证工作

样品：山东东明县采集样品，750 dyslexics，750 controls

位点：
1）芯片筛选到的p value<10^{-4}的位点68个；
2）ROBO1, DCDC2, KIAA0319和DYX1C1基因上Tag SNP总计30个。

显著性易感位点1(2.45E-5)

Gene A ，内含子区域

显著性易感位点2(2.64E-5)

Gene B，内含子区域

显著性易感位点3(8.95E-5)

Inter-genetic region 基因间区域

Preliminary findings:

- Two genes have been identified. These two genes have not been reported in the literature, so they might be specific to Chinese dyslexia
- Their functions are to be explored
- Whether the two genes are linked to the language-specific brain regions are unknown.
- The four known genes (ROBO1, DCDC2, KIAA0319, DYX1C1) causing alphabetic language reading disorders have not been confirmed.

China's National Key Basic Research Program Grant ("973" program grant)

Brain mechanisms underlying Chinese language processing and the neurogenetic basis for its disorder (2012CB720700)

1/2/2012 – 31/8/2016 (budget limit: RMB39M + a matching fund)
中国语言相关脑功能区与语言障碍的关键科学问题研究

Chief scientist: Tan Li-Hai
Major participants:
HKU (subproject 1)
Beijing Institute of Tech (subproject 2)
CapitalBio Company and Tsinghua Univ (subproject 3)
Beijing 306 Hospital (subproject 4)
Qsinghua Univ Yuquan Hospital
Chinese U of HK (William Wang & Gang Peng)
Peking Univ
MIT

973 CHINA
国家重点基础研究发展计划

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謝謝！