Novel approaches for investigating brain function in health and disease using simultaneous MR-PET imaging

Gary F. Egan

Monash Biomedical Imaging, Monash University & Australian Research Council Centre of Excellence for Integrative Brain Function, Melbourne, Australia.

Despite the apparent ubiquity of the use of BOLD-fMRI for studying human brain function over the last 25 years, the method has a number of shortcomings. The most significant shortcoming of BOLD-fMRI is that the method is not a direct or quantitative measure of neuronal activity.

The investigation of higher-order cognitive functions in the normal human brain, including attention, memory and executive function, involve experimental paradigms and manipulations that result in coupled responses of the concurrent BOLD and FDG signal changes. Conversely, the uncoupling of changes in blood oxygenation and glucose metabolism are thought to underlie many of the cognitive deficits seen in ageing, neurodegenerative diseases and psychiatric conditions.

Furthermore, changes in dynamic regional glucose metabolism may even precede structural, functional and cognitive symptoms in some disease conditions. The technological developments that have led to MR-PET scanners have now made it possible to simultaneously examine changes in blood oxygenation and glucose metabolism at rest, or in response to a stimulus/task, using simultaneously acquired BOLD-fMRI and FDG-PET datasets.

This presentation will outline novel approaches for investigating brain function in health and disease using simultaneous BOLD-fMRI and FDG-PET brain mapping studies.
A retinoraphe projection regulates serotonergic activity and looming-evoked defensive behavior

Kwok Fai So

The University of Hong Kong

Animals promote their survival by avoiding rapidly approaching objects that indicate threats. In mice, looming-evoked defensive responses are triggered by the superior colliculus (SC) which receives direct retinal inputs. However, the specific neural circuits that begin in the retina and mediate this important behaviour remain unclear. Here we identify a subset of retinal ganglion cells (RGCs) that controls mouse looming-evoked defensive responses through axonal collaterals to the dorsal raphe nucleus (DRN) and SC. Looming signals transmitted by DRN-projecting RGCs activate DRN GABAergic neurons that in turn inhibit serotoninergic neurons. Moreover, activation of DRN serotoninergic neurons reduces looming-evoked defensive behaviours. Thus, a dedicated population of RGCs signals rapidly approaching visual threats and their input to the DRN controls a serotonergic self-gating mechanism that regulates innate defensive responses. Our study provides new insights into how the DRN and SC work in concert to extract and translate visual threats into defensive behavioural responses.
What is so special about the human brain?

Sir Colin Blakemore

Professor of Neuroscience & Philosophy, School of Advanced Study, University of London
&
Emeritus Professor of Neuroscience, University of Oxford

It seems obvious that the special characteristics of the human mind result from the enlargement of the brain during hominid evolution. The human brain is very big, but not as large as the brain of an elephant, some species of whale, or even Neanderthal man. The fundamental features of our nerve cells and our cerebral cortex are very similar to those of a mouse, and most of the so-called unique characteristics of human cognition have been demonstrated in other species. Yet there clearly is something distinctive about human beings. Elephants can’t talk. Whales haven’t invented science. And we got rid of Neanderthal man! Moreover, the crucial genetic changes that created the human species occurred more than 200,000 years ago, yet our present-day culture is utterly different from that of our Stone-Age ancestors. Conventional natural selection is not responsible for the emergence of the modern mind. What could have driven the evolution of culture?
The human neuroimaging literature uses standardized coordinates (x-y-z addresses for brain locations) for extracting and reporting neural effects of task performance, regional functional and structural alterations in neuropsychiatric disorders, treatment effects, and so forth. Coordinate-based meta-analysis (CBMA) quantitatively explores this large (> 40,000 studies) and rapidly growing literature to identify observations which are consistently observed across sites and samples. That is, CBMA provides an immediate solution to the much-discussed fMRI “false positive problem”. The algorithm most widely used for CBMA is activation likelihood estimation (ALE). CBMA can also be used to extract network properties by computing cross-study, inter-regional co-variances, both functional and structural, termed meta-analytic connectivity modeling (MACM). MACM can be performed within multiple computational frameworks including ALE, structural equation modeling (SEM), graph theoretical modeling (GTM), and independent components analysis (ICA). Transdiagnostic analyses — identifying neurobiological commonalities across disparate psychiatric and neurologic diagnostic categories — is an emerging, highly impactful application of meta-analytic modeling. Further, quantitative comparisons of ICA-derived transdiagnostic structural covariance networks with functional covariance (co-activation) networks lends strong support to the Network Degeneration Hypothesis, as proposed by Seeley and colleagues.
Neural Repair strategy for the treatment of neurological and psychiatric diseases

Bai Lu

School of Pharmaceutical Sciences, Tsinghua University, Beijing, China, 100084

Neurodegenerative diseases (ND) such as Alzheimer’s disease (AD) and Amyotrophic lateral sclerosis (ALS) are devastating illnesses with no treatment. Therapeutic strategy targeting pathogenic toxins (such as amyloid β) has so far been unsuccessful. A paradigm shift is needed to meet the huge challenges. We have proposed to target pathophysiology (anti-inflammation, synaptic repair, etc.) instead of pathogenesis (toxin-reduction) (Lu, Nature Rev. Neurosci. 2013). BDNF is by far the best-known “synaptogenic” molecule and perhaps the only one proven to facilitate synaptic function in human. Animal studies have demonstrated that BDNF modulates synaptic transmission, synaptic plasticity and synaptogenesis, and protect synaptic loss due to toxic insults in neurodegenerative diseases. Increasing evidence points to genetic epistasis between BDNF Val/Met polymorphism and “disease genes” in ND endophenotypes such as episodic memory and hippocampal volume in humans. However, the physicochemical properties of BDNF have hampered BDNF itself to be developed as a therapeutic agent, and the few clinical trials have all been disappointing.

Agonistic antibodies specific for TrkB can mimic BDNF function by dimerizing TrkB receptor and activate its downstream signaling pathways. We have conducted a systematic screening of TrkB agonist antibodies (TrkB-AgoAbs) and identified a number of candidates with biological functions similar to BDNF but outstanding pharmacokinetics (PK) and low effective concentrations. These candidates exhibit several distinctive features superior to BDNF: (1) Unlike BDNF which is a highly charged molecule difficult to diffuse, TrkB-AgoAbs are easily diffusible. (2) BDNF activates not only TrkB but also p75NTR; the latter results in neuronal death and synaptic inhibition. In contrast, TrkB-AgoAb is highly specific for TrkB. (3) The half-life of BDNF is a few hours while that of TrkB-AgoAb is several weeks. Moreover, we have identified TrkB-AgoAbs that bind to epitopes distinct from the BDNF-binding site on the TrkB extracellular domain.

Investigation of the biological and pharmaceutical properties of the TrkB-AgoAb candidates has been systematic performed using in vitro and in vivo models for multiple NDs. For ALS, TrkB-agoAb induced TrkB phosphorylation, and activated all three TrkB signaling pathways, and reduced apoptosis induced by serum deprivation in culture motor neurons. TrkB-AgoAb candidates enhanced the survival and promoted the neurite outgrowth in the TrkB-expressing PC12 cells, cultured hippocampal and cortical neurons, spinal motor neurons and retinal ganglion neurons. TrkB-AgoAb also enhanced neuronal survival in the motor neuron degeneration model of spinal root avulsion injury, glaucoma model of elevated intraocular pressure, and stroke model of MCAO. Moreover, TrkB-AgoAb was detected in brain tissues with efficient concentration when it was injected through tail vein. Taken together, TrkB-AgoAb may be an excellent drug candidate for various neurodegenerative diseases.
How do native speakers process sentences with little lexical conceptual information?: An eye-tracking investigation on processing for Japanese scrambled sentences

Katsuo Tamaoka and Michael Mansbridge

Nagoya University, Japan

The syntactic movement of scrambled Japanese sentences is often attributed to pre-head anticipatory processing prior to reading the head verb. However, previous studies did not compare nouns within the same sentence position and, furthermore, compared different nouns types, thus influencing processing via semantic activation. Therefore, this study only presented highly frequent first names and kept each noun in the same position by only manipulating the case markings. Under this strictly-controlled condition which contained little lexical conceptual information, scrambling was investigated using two eye-tracking experiments. The results indicated pre-head processing begins establishing the filler-gap dependency at critical NP containing the gap as revealed by significantly longer go-past times for scrambled conditions. However, without additional semantic cues, case marking alone could not provide enough information as seen by the difficulties for scrambled conditions during late-processing stages at the critical NP after reading the verb. Specifically, Japanese speakers were largely required to utilize verb information for establishing the structural and semantic properties of scrambled constituents. Consequently, the relative strength of pre-head and head-driven processing varies depending on the cues available.
Functional Near Infrared Spectroscopy: an emerging technique in the neuroscience field

Willy NJM Colier

Artinis Medical Systems BV
Einsteinweg 17, Elst, the Netherlands
w.colier@artinis.com

In 1977 the first publication on the technique of near infrared spectroscopy (NIRS) was published in Science by Frans Jobsis-van der Vliet. The first publication on functional NIRS came out in 1993 and was published by prof. Mamura Tamura in Japan. The NIRS technique is based on the relative transparency of human tissue for light in the 700-900 nm region as well as the oxygen dependent light absorption of oxyand deoxyhemoglobin. In combination with the haemodynamic or blood oxygen level dependent (BOLD) response, which is also the basis of the fMRI technique, we have a powerful tool for neuroscience research. In the last decade fNIRS has really taken of. It is predicted that within 2 or 3 years there will be more fNIRS papers than there will be fMRI papers! In this talk I will address some of the recent developments which made it possible for NIRS to make the transition from a toy for a limited number of users to a tool in the hands of many researchers in very different fields.

An important factor in all this was the development of much more portable equipment towards nowadays fully wireless equipment, which has given an enormous boost to the fNIRS community. Measurements can be done in real life situations, something impossible with fMRI. This opens up new fields for research in e.g. young children and elderly, previously difficult to perform with fMRI. It is even possible to research multiple subjects at once who can interact with each other in a natural environment. This technique is called hyperscanning.

Besides instrumental developments there have been many methodological improvements. One of these topics is the short channel separation, or reference channel: by introducing an optical channel at a (debatable) short distance, e.g. 10 mm, one should in principal be able to correct for influences of the extra-cerebral contamination of the haemodynamic response. Ideally this should improve signal quality of your fNIRS measurements.

And lastly, the combination of (f)NIRS with other imaging modalities is very promising. In the past integration of different methodologies used to be cumbersome but more and more handy solutions are brought to market by the various manufacturers of this type of equipment.
How do the Hierarchical Levels of Premises Affect Category-based Induction: Diverging Effects from the P300 and N400

Yi Lei¹,²,³, Xiuling Liang³,⁴ & Chongde Lin⁵

¹College of Psychology and Sociology, Shenzhen University, Shenzhen, 518060, China. ²Shenzhen Key Laboratory of Affective and Social Cognitive Science, Shenzhen, 518060, China. ³Center for Language and Brain, Shenzhen Institute of Neuroscience, Shenzhen, 518057, China. ⁴School of Medicine, Shenzhen University, Shenzhen, 518060, China. ⁵School of Psychology, Beijing Normal University, Beijing, 100875, China.

No 3688, Nanhai Road, Nanshan District, Shenzhen, China, 518060
leiyi821@vip.sina.com

Objective

Although a number of studies have explored the time course of category-based induction, little is known about how the hierarchical levels (superordinate, basic, subordinate) of premises affect category-based induction. The main purpose of this study was to explore how hierarchical levels of premises modulated category-based induction at behavioural and electrophysiological levels.

Methods

Nineteen healthy, right-handed volunteers (eleven females), between the age of 19 and 26 (21.58 ± 1.96, mean ± SD), took part in the task. The present experiment used a single premise category-based induction task with a blank property which is represented by capital letters ranging from A to Z, in order to reduce the memory load and background knowledge effect. The hierarchical levels of premises and conclusions (superordinate, basic, and subordinate) were manipulated.

Results & Discussion

The ERP results showed that: in the subordinate conclusion condition, the basic premise elicited a larger N400, versus the superordinate premise; in the basic conclusion condition, the superordinate premise elicited a larger P300 relative to both the basic premise and subordinate premise; in the superordinate conclusion condition, however, no difference was found between different premises. Furthermore, the process that reasoning from a higher level to a lower level evoked a larger P300, compared to it did in the reverse direction.

Conclusions

The divergent evidence suggested that category-based induction at superordinate, basic, and subordinate levels might be affected by various factors, such as abstract level, direction, and distance between premise and conclusion, which yielded new insights into the neural underpinnings of category-based induction with different inductive strengths.
The role of sentence-final particle -ne in Japanese for constructing interpersonal relations

Sachiko Kiyama

Tohoku University

Some East and South-East Asian languages have sentence-final particles (SFPs) to yield various discourse functions. Particularly in Japanese, SFPs such as -ne and -yo have no obvious effect on the truth conditions of a sentence, but they encompass a diverse range of usages, from typical to atypical, according to the context and the interpersonal relationships in the specific situation. The most frequent particle, -ne, is typically used after addressee-oriented propositions for information sharing, while another frequent particle, -yo, is typically used after addresser-oriented propositions to elicit a sense of strength. In this talk, I will show findings from ERP experiments (Kiyama, et al., 2018, Journal of Neurolinguistics), which reveal individual differences among native speakers in flexibly understanding the addressee-oriented -ne based on their mentalizing ability (i.e., the ability to infer the mental states of others). This result plausibly reflects low-ability mentalizers' stronger sense of strangeness toward atypical -ne usage. While high-ability mentalizers may aptly perceive others' attitudes via their various usages of -ne, low-ability mentalizers seem to adopt a more stereotypical understanding. These results attest to the greater degree of difficulty low-ability mentalizers have in establishing a smooth regulation of interpersonal distance during social encounters.
TMC proteins modulate membrane excitability through a background sodium-leak conductance

Xiaomin Yue, Jian Zhao, Xiao Li, Hu Zhang, Duo Duan, Xiaoyan Zhang, Wenjuan Zou, Yadan Xue, Yi Sheng, Ting Zhang, Qian Yang, Jianhong Luo, Shumin Duan, Rui Xiao, Lijun Kang

Department of Neurobiology, Institute of Neuroscience, Key Laboratory of Medical Neurobiology of the Ministry of Health of China, Zhejiang University School of Medicine
Research Building A416, Institute of Neuroscience, School of Medicine, Zhejiang University, No. 866 Yu Hang Tang Rd. Hangzhou, China
yuexiaomin@126.com

Membrane excitability is a fundamentally important feature for all excitable cells, including both neurons and muscle cells. However, the background depolarizing conductances in excitable cells, especially muscle cells, are not well characterized. Although mutations in transmembrane channel-like (TMC) proteins TMC1 and TMC2 cause deafness and vestibular defects in mammals, their precise action modes are elusive. Here, we discover that both TMC-1 and TMC-2 are required for normal egg laying in C. elegans. Mutations in these two TMC proteins cause membrane hyperpolarization and disrupt the rhythmic calcium activities in both neurons and muscles involved in egg laying. Mechanistically, TMC proteins enhance membrane depolarization through sodium-leak currents and ectopic expression of TMC-1 in TMC-negative neurons results in the sodium-dependent membrane depolarization. Therefore, we have identified an unexpected role of TMC proteins in modulating membrane excitability. Our results may provide mechanistic insights into the functions of TMC proteins in hearing loss and other diseases.

REFERENCE


Pan et al., (2013). TMC1 and TMC2 are components of the mechanotransduction channel in hair cells of the mammalian inner ear. Neuron 79, 504-515.

The effects of apolipoprotein E on default mode network in Alzheimer’s disease spectrum

Yao Zhu, Liang Gong, Qingguo Ren, Chunming Xie

Department of Neurology, Affiliated ZhongDa Hospital, Southeast University
No.87, Dingjiangiao, Gulou District, Nanjing City, China.
zyao105@sina.com

Previous studies that investigated the effects of apolipoprotein E (APOE) ε4 status on default mode networks (DMN) and its disruption due to the presence of a disease such as Alzheimer’s disease (AD). Exploring DMN functional connectivity (FC) changes of APOE isoform population across the Alzheimer’s disease spectrum might provide valuable evidence for better understanding the development of AD. Magnetic resonance imaging data and neuropsychological test scores from 169 subjects (CN = 46, EMCI = 52, LMCI = 41, AD = 30) were obtained from the Alzheimer’s Disease Neuroimaging Initiative. Posterior cingulate cortex seed-based FC analysis was used to obtain the DMN patterns. The results indicated that the trend for changed DMN FC strength was opposite in ε4 carriers compared to ε4 non-carriers across the Alzheimer’s disease spectrum patients. Specifically, the increases in posterior cingulate cortex FC with the right precuneus, insular, fusiform were positively correlated with the changes in mini-mental state examination (MMSE) in ε4 non-carriers across the Alzheimer’s disease spectrum. Furthermore, Conditional analysis revealed that connectivity strength regulates the effects of APOE genotype on cognitive function across the Alzheimer’s disease spectrum. Our findings suggest that APOE ε4 carriers and non-carriers present both increased and decreased functional connectivity in DMN across the Alzheimer’s disease spectrum, which is correlated with clinical cognitive performances. DMN FC changes might be an early sign for cognitive decline.
Disrupted functional connectivity patterns of insula subregions in major depressive disorder

Chao Wang¹,², Huawang Wu⁴, Jiaojian Wang³, Hong Li¹,²

¹College of Psychology and Sociology, Shenzhen University, Shenzhen, 518060, China, chao.wang159@gmail.com
²Shenzhen Key Laboratory of Affective and Social Cognitive Science, Shenzhen University, Shenzhen, 518060, China
³Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, 625014, China
⁴Department of Radiology, The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huai Hospital), Guangzhou, 100053, China

Major depressive disorder (MDD) is characterized by impairments in emotional and cognitive functions. Emerging studies have shown that cognition and emotion interact by reaching identical brain regions, and the insula is one such region with functional and structural heterogeneity. Although previous literatures have shown the role of insula in MDD, it remains unclear whether the insular subregions show differential change patterns in MDD. Using the resting-state fMRI data in a group of 23 drug-free MDD patients and 34 healthy controls (HCs), we investigated whether the abnormal connectivity patterns of insular sub-regions or any behavioural correlates can be detected in MDD. Further hierarchical cluster analysis was used to identify the functional connectivity-clustering patterns of insular sub-regions. Compared with HCs, the MDD exhibited higher connectivities between dorsal agranular insula and inferior parietal lobule and between ventral dysgranular and granular insula and thalamus/habenua, and lower connectivity of hypergranular insula to subgenual anterior cingulate cortex (Figure 1). Moreover, the three subregions with significant group differences were in three separate functional systems along anterior-to-posterior gradient (Figure 2). The anterior and middle insula showed positive correlation with depressive severity, while the posterior insula was to the contrary (Figure 1). These findings provided evidences for the MDD-related effects in functional connectivity patterns of insular subregions, and revealed that the subregions might be involved in different neural circuits associated with the contrary impacts on the depressive symptoms.
A Word That Matters: Distinctive Neural Responses of Affirmative and Negative Sentences across Two Languages

Hao Yan¹,²*, Yingying Huang¹
1. Department of Linguistics, Xidian University
Xi’an710071, China
2. Center for Language and Brain, Shenzhen Institute of Neuroscience
Shenzhen 518057, China
yanhao@xidian.edu.cn

Because of its uniqueness in human communication system, sentential negation is a very interesting and important issue in cognitive science. A great challenge to the truth reversing theory was that previous studies failed to separate contribution of the truth reversing process from that of other factors, such as the number of words /sentence length, syntactic complexity, and surface structure of sentential negation. The present study is aimed at probing neural mechanisms underlying affirmative and negative sentences by matching both sentence length and syntactic complexity in two languages. Given that Chinese and English represented two distinct language systems in realizing sentential negation, we also examined if bilinguals processed affirmative and negative sentences differently. We found that negatives produced greater activation than affirmatives in areas of the left inferior gyrus (IFG, BA47), the left middle temporal gyrus (MTG, BA21), bilateral superior temporal gyrus (STG, BA42), bilateral inferior parietal lobule (IPL, BA40) and dorsal anterior cingulate cortex (dorsal ACC). It reflected different semantic entailment directions between the two types of sentences, and suggested involvement of cognitive control during the truth-reversing process. Meanwhile, the English > Chinese contrast activated the right superior and left middle frontal gyrus (S/MFG, BA 8/10), the right post central gyrus (PstCG, BA 2), bilateral superior parietal gyrus (SPL, BA 7) and the right anterior cingulate cortex (ACC), which implement phonology analysis of alphabetical languages. This native-like brain activity extended the assimilation/accommodation theory to the syntax aspect. Furthermore, we found interaction effects between sentence type and language in areas of the anterior prefrontal cortex (BA10/46), inferior frontal gyrus (BA45/47) and MTG (BA21). This interaction suggested that negative processing was affected by language features, and pointed to potential neural biomarkers that could differentiate brain activity pattern of English and Chinese in bilinguals.

Keywords: affirmative sentences, negative sentences, Chinese-English bilinguals, neural biomarker, brain imaging

Fig.4: Cortical regions that showed distinctive neural responses of affirmative and negative sentences across the two languages. (i) Cortical regions that showed an interaction effect of language and sentence type included the right pars triangularis (BA45) and left pars orbitalis (BA47) in the inferior frontal gyrus (IFG), the left MFG (BA46), the right medial frontal gyrus (MeFG, BA10), the bilateral anterior prefrontal cortex (PFC, BA10), and the right MTG (BA20). (ii) Simple effect analysis of beta values extracted from these 7 ROIs was displayed in two middle columns. (iii) “*” indicates significant threshold of p<0.05; “**” indicates significant threshold of p<0.01; and “***” means p<0.001.
Anxious Brain Networks: A Coordinate-Based Meta-analysis of Resting-State Functional Connectivity Studies in Anxiety Disorders

Pengfei Xu

Shenzhen Key Laboratory of Affective and Social Neuroscience, Shenzhen University, Shenzhen 518060, China
Center for Emotion and Brain, Shenzhen Institute of Neuroscience, Shenzhen 518057, China
#B610 Shenzhen Virtual University Park Key Laboratory Platform, No.6 Yuexing 2nd Road, Nanshan District, Shenzhen, Guangdong Province, P.R. China 518057
xupf@szu.edu.cn

Anxiety disorders have been characterized pronounced alterations to resting brain networks, including the executive control network (ECN), salience network (SN), ventrally attention network (VAN), and default mode network (DMN; Sylvester et al., 2012). Although somewhat informative, prior resting-state functional connectivity studies have focused predominantly on specific clinical groups and/or state/trait anxiety, with fragmentary and heterogeneous findings. The present meta-analysis aimed to summarize disorganized brain networks in anxiety and anxiety disorders through a meta-analysis of seed-based whole-brain RSFC studies.

A comprehensive search was conducted by using Web of Science and PubMed with the keywords “anxiety OR anxious AND rest OR resting AND connect OR connectivity”. Original functional magnetic resonance imaging (fMRI) studies using seed-based whole-brain RSFC to compare anxiety disorders (e.g., generalized anxiety disorder, social anxiety disorder, specific phobia, panic disorder) with healthy controls (HC), as well as studies of HCs wherein anxiety was measured (e.g., State-Trait Anxiety Inventory, Liebowitz Social Anxiety Scale, and Hamilton anxiety rating scale) were eligible for inclusion. Twenty-four studies were included in the meta-analysis. Sixty-eight seeds were categorized into five seed-networks (affective network - AN, ECN, SN, VAN, and DMN). Peak coordinates of significant group differences (319 contrasts) were extracted and converted to MNI space. Hyper-connectivity (increased positive or reduced negative connectivity) or hypo-connectivity (increased negative or reduced positive connectivity) between or within these networks in anxiety and ANX were calculated via activation likelihood estimation (ALE) algorithm (Eickhoff et al., 2012). Multiple comparisons correction was implemented using Gaussian Random Field Theory with conservative cluster determining (i.e., p < .001) and extent thresholds (i.e., k >= 200 mm3) by using the GingerALE 2.3.6 software (http://brainmap.org/). Results showed that anxiety was characterized by hypo-connectivity between the AN and the ECN, and between the AN and the DMN that involved in regulation of emotion, and between the DMN and the ECN, and between the SN and the sensorimotor network (SMN), and hypo-connectivity within the SN.

The present meta-analysis provides quantitative neuroimaging evidence of large-scale alterations to brain networks across anxiety. These results capture the diverse character of anxiety disorders and provide a foundation for the neurocognitive basis to symptom presentation across trait anxiety and anxiety disorders. These findings provide an empirical foundation for a neurocognitive model in which network dysfunctions underlie core cognitive and affective abnormalities in anxiety and AD and will benefit to develop novel network-based treatment strategies for AD.

Reference


Decoding the intensity of sensory input by one *C. elegans* interneuron to regulate two types of behavioral outputs

Haining Zhang¹,²,*, Jiajun Fu¹,⁴,*, Wenjuan Zou³,*, Kang Du², Wenming Huang², Junwei Yu¹, Howard A. Baylis⁵, Wei Ji¹, Lijun Kang³ and Tao Xu¹,²,⁴

¹ National Laboratory of Biomacromolecules, CAS Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China

² Key Laboratory of Molecular Biophysics of the Ministry of Education, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China

³ Department of Neurobiology, Institute of Neuroscience, Key Laboratory of Medical Neurobiology of the Ministry of Health of China, Zhejiang University School of Medicine, Hangzhou 310058, China

⁴ College of Life Sciences, University of Chinese Academy of Sciences, Beijing 100049, China

⁵ Department of Zoology, University of Cambridge, Cambridge CB2 3EJ, United Kingdom.

Address: 866, Yuhangtang Road, Hangzhou, Zhejiang Provence

zouwenjuan2008@163.com

How neurons are capable of decoding stimulus intensity and translate this information into multiple behavioral outputs is poorly defined. Here, we demonstrate that the *C. elegans* interneuron AIB regulates two distinct behaviors: reversal initiation and feeding suppression in response to different concentration of quinine. Low concentrations of quinine are decoded in AIB by a high affinity glutamate receptor GLR-1 and translated into reversal initiation. In contrast, high concentrations of quinine are decoded by a low affinity, kainate-type ionotropic glutamate receptor GLR-5 in AIB. GLR-5 activation evokes sustained Ca²⁺ release from inositol 1,4,5-trisphosphate (IP₃)-sensitive Ca²⁺ stores and neuropeptide release, which in turn activates the downstream neuron RIM and inhibits feeding. Our results reveal that different signal patterns in AIB-RIM connection encode distinct behavioral outputs depending on the intensities of sensory input, highlighting the importance of functional mapping of information propagation at the single-neuron level in connectome construction.
Alleviation of Mechanical Allodynia Produced by 14,15-epoxyeicosatrienoic Acid in a Central Post-stroke Pain Model: Possible Role of Allopregnanolone and δGABAARs

Xuhui Chen, Bo Zhang, Wenlong Yao, Chuanhan Zhang, Li Wan, Yue Zhang
Department of Anaesthesiology and Pain Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.
Jiefang Avenue 1095, 430030, Wuhan, Hubei Province, PR China
chenxh_2016@126.com

Background: Stroke is the leading cause of disability worldwide, and most survivors suffer from central post-stroke pain (CPSP). Accumulating evidence indicates that epoxyeicosatrienoic acids (EETs) display antinociceptive effects in the spinal and ventrolateral periaqueductal grey. However, the role of 14,15-EET in the development and maintenance of CPSP remains largely unknown.

Methods: Pain-related behaviour levels of 14,15-EET and AP, and expression of StAR and δGABAAR in the medial thalamus (MT) of CPSP rats displaying allodynia were analysed at different time points after CPSP. Then, 14,15-EET (0.025, 0.05, 0.1 µg/µl) or vehicle (β-cyclodextrin, 1 µl), 5α-reductase inhibitor or antagonist of GABAAR was administered to test the anti-nociception of 14,15-EET, and we also compared the analgesic effect of 14,15-EET with those of gabapentin.

Results:
Thalamic haemorrhagic stroke induced mechanical allodynia (Fig. 1) and a significant decrease in the levels of StAR, AP and δGABAAR in the MT (Fig. 2);

![Fig. 1. *P < 0.05, **P < 0.01, # P < 0.05, compared with ITS rats; Fig. 2. *P < 0.05, **P < 0.01, ***P < 0.001 compared with the ITS group.](image)

Behavioural studies showed that intrathalamic injection of 14,15-EET (0.1 µg) during the acute stage of stroke significantly alleviated mechanical allodynia (Fig. 3) by increasing the levels of StAR, AP and δGABAAR (Fig. 4);

![Fig. 3. *P < 0.05, **P < 0.01, ***P < 0.001 compared to the vehicle group; Fig. 4. *P < 0.05, **P < 0.01, ***P < 0.001 compared with the vehicle group.](image)

However, this protective effect could be partially attenuated by 5α-reductase enzyme inhibitors (finasteride and dutasteride) (Fig. 5) and an antagonist of GABAAR (bicuculline) (Fig. 6);

![Fig. 5. *P < 0.01, **P < 0.01, ***P < 0.001 compared to the vehicle group; Fig. 6. &P < 0.05 compared with the ITC + EET + BIC group.](image)

Moreover, the anti-nociception effect of early treatment with 14,15-EET was more effective than that of GBP (60 mg/kg) in CPSP rats (Fig. 7);

![Fig. 7. &P < 0.05, &&P < 0.01, &&&P < 0.001 compared with GBP group.](image)

Conclusion: Our findings indicate that reduction of AP and δGABAAR levels in the MT was involved in the development and maintenance of CPSP. Moreover, 14,15-EET may be an effective treatment strategy for CPSP that both promotes AP production via upregulation of StAR and increases the expression of δGABAAR in the MT, alleviating CPSP.
Brain activation and functional connectivity underlying Chinese writing: an fMRI study

Yang Yang¹,²

¹Center for Brain Science and Learning Difficulties, Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China
²Center for Language and Brain, Shenzhen Institute of Neuroscience, Shenzhen 518057, China yangyang@psych.ac.cn

Writing is a complex process that involves language, cognition and perceptual-motor skills. How the brain processes writing in Chinese, a logographic writing system that dramatically differs from alphabetic languages, is largely unknown. Using functional magnetic resonance imaging (fMRI), this study examined the brain activation and functional connectivity that underlies actual Chinese writing in right-handed adults using two conditions: writing to dictation of Chinese characters and drawing circles. When compared to drawing circles, writing Chinese characters recruited greater activations in the bilateral precentral gyrus, superior/medial frontal gyrus, fusiform gyrus, cerebellum and the left superior parietal lobule than drawing circles that were associated with the spelling and motor processes of writing. Importantly, functional connectivity analysis was also used for further characterization of the neural circuits specific to Chinese writing. Functional connectivity was observed between the left precuneus and the left premotor area and the bilateral cerebellum that likely supports motor processing, whereas functional connectivity observed between the right fusiform gyrus and bilateral inferior/middle occipital gyrus that likely supports spelling processing. These findings illustrate the neural mechanisms of actual Chinese writing for the first time, extending our knowledge of the cognitive processing required for this form of human communication.

key words: Chinese writing, fMRI, brain activation, functional connectivity
Interpersonal Brain Synchronization between Individuals Acting Differently in the Complementary Collaboration

Xiaojun Cheng1,2, Yinying Hu2, Yi Zhu2, Yafeng Pan2, Yi Hu2

1 College of Psychology and Sociology, Shenzhen University, Shenzhen, China
2 School of Psychology and Cognitive Science, East China Normal University, Shanghai, China.
chengxiaojun@szu.edu.cn

In the complementary collaboration, people act differently to attain the shared goal. However, the effect of their action discrepancy on the collaboration is not well understood. In this study, participant dyads co-drew shapes of parallelogram on the computer (i.e., one controlled the horizontal movement and the other controlled the vertical), either at the same speeds (less discrepancy, LD) or at different speeds (more discrepancy, MD) (Figure B). The brain activities were simultaneously recorded by the functional near-infrared spectroscopy (fNIRS) based hyperscanning technique (Figure A). Results showed that there was better collaborative performance in the MD condition than that in the LD condition. In the MD condition, the better performance was further found to be associated with the interpersonal brain synchronization (IBS) between participants at the frontopolar areas (Figure C/D/E). Further analyses on the IBS showed its relation to the dyads’ self-control conception and that if the brain influence from one participant to the other participant went stronger the reversed influence would be stronger too. In contrast, these findings were not found in the LD condition. Taken together, our study reveals the brain-to-brain mechanism in the complementary collaboration when individuals act more differently, providing evidence for the theory that diversity among persons favors for the collaboration, and suggests the positive role of self-control conception in the efficient team work.
Motion Detection and Action Recognition Based on Upper Extremity Movement Score

Shaofa Chen¹,Qiang Ma¹,Junhao Zhao¹,Jie He¹,Guo Dan¹,²,³

¹. School of Biomedical Engineering, Shenzhen University, Shenzhen, Guangdong, 518060; ². Shenzhen Academy of Neurosciences, Shenzhen, Guangdong, 518057; ³. Correspondence author

Abstract:Objective:A method for automatic detection and recognition of movements with different grading levels in the same movement in the upper limb of Fugl-Meyer is studied.

Methods:The system adopts a set of motion acquisition module based on nine-axis sensor MPU9250, which can collect the information of acceleration, angular velocity and magnetic force of the patient during the course of motion. The sensor is worn on the wrist of the experimenter. It is transmitted to the computer via wireless Wi-Fi. The computer receives the data from the sensor and detects the movement of the subjects. When a complete motion is detected, Actions are identified to distinguish three different levels of movement in the upper limb of the FMA.

Results:For three different difficulty classes of the same upper limb movement, the average recognition rate of the system is 98.68.

Conclusion:This method can be used to evaluate the function of upper limb of FMA in stroke patients.

<table>
<thead>
<tr>
<th>project</th>
<th>Total number of movements</th>
<th>Action detection number</th>
<th>False detection number</th>
<th>Action detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 kinds of difficulty of hand touching lumbar vertebrae</td>
<td>300</td>
<td>298</td>
<td>2</td>
<td>99.33%</td>
</tr>
<tr>
<td>3 difficulties of shoulder flexion</td>
<td>300</td>
<td>300</td>
<td>0</td>
<td>100.00%</td>
</tr>
<tr>
<td>3 kinds of difficulty of forearm pronation</td>
<td>300</td>
<td>301</td>
<td>1</td>
<td>99.67%</td>
</tr>
<tr>
<td>total</td>
<td>900</td>
<td>899</td>
<td>3</td>
<td>99.89%</td>
</tr>
</tbody>
</table>

reference


Effective connectivity for resolving conflict of linguistic information in word reading

Min Xu¹,²,³, Wai Ting Siok²,⁴ & Li Hai Tan¹,²,³

¹Neuroimaging Laboratory, School of Biomedical Engineering, Shenzhen University Health Science Center, Shenzhen, China.
²State Key Laboratory of Cognitive Neuroscience and Learning at Shenzhen, Shenzhen Institute of Neuroscience, Shenzhen, China
³Center for Brain Research, Beijing Normal University, Beijing, China
⁴Department of Linguistics, University of Hong Kong, Hong Kong

xumin@szu.edu.cn; siok@hku.hk; tanlh@szu.edu.cn

Introduction. The skill of linking orthography with phonology is essential for reading acquisition across writing systems¹. Previous neuroimaging studies have examined the interaction of orthographic and phonological information during reading by manipulating the conflict between them, showing that the subjects recruited the brain regions mediating orthographic and phonological processing to a greater extent to resolve the conflict²,³. However, one important question remaining unsolved is how the brain regions for conflict processing, such as the anterior cingulate cortex (ACC)⁴,⁵, might interact with the reading-related brain systems to resolve the conflict during reading.

Methods. In the present functional magnetic resonance imaging (fMRI) study, we used dynamic causal modelling and investigated the effective connectivity between the ACC and reading-related cortical regions during orthography-phonology conflict processing of Chinese word.

Results and Conclusions. We found that the cortical activation in brain regions including the left ventral occipitotemporal cortex (vOT), left middle frontal gyrus (MFG) and left posterior parietal cortex may reflect conflict-driven augmentations of neural representations of the orthographic and phonological information. In the conflict condition, ACC received reduced information from the left vOT and increased information from the left MFG, which might reflect less reliance on information of visual word form representation but more reliance on accurate integration between orthography and phonology to resolve the conflict. The findings provide important insight into how the brain adjusts to resolve conflict in the language domain.

Reference:
Development of Lower Limb Motor Nerve Function Rehabilitation Training Based on Upper Extremity Motion Information

Junhao Zhao, Guo Dan

School of Biomedical Engineering, Shenzhen University
No. 3688 Nanhai Road, Nanshan District, Shenzhen, Guangdong
zhaobling@gmail.com

Stroke patients showed unilateral hemiplegia in limb dysfunction, and the other limb was more flexible. This study is expected to design a gait rehabilitation training platform based on inertial sensors. In the gait rehabilitation training robot has a passive training mode, active training mode, based on an additional side of the body control training mode.

The motion control module is the core module of the entire control system. Each sub-module is closely linked around the motion control module. It receives command information of the human-computer interaction module, acquires motion status information of the robot, collects sensor status signals, and makes control decisions, and implements core algorithms such as speed planning, trajectory planning, and interpolation calculation, thereby controlling the drive of the drive motor to perform corresponding operations. Makes the lower extremity exoskeleton rehabilitation robot to successfully complete the rehabilitation training according to the procedure specified by the operator. The overall framework of this design is shown in Figure.

reference
Differences in phonological properties of the same logographic writing system modulate the cortical activation of second language in bilinguals

Zhenglong Lin\textsuperscript{1,2}, Geqi Qi\textsuperscript{3}, Jiajia Yang\textsuperscript{4}

\textsuperscript{1}Neuroimaging Laboratory, School of Biomedical Engineering, Shenzhen University Health Science Center, Shenzhen, China
\textsuperscript{2}State Key Laboratory of Cognitive Neuroscience and Learning at Shenzhen, Shenzhen Institute of Neuroscience, Shenzhen, China
\textsuperscript{3}Department of Psychology, College of Education Science, Inner Mongolia Normal University, Huhhot, China
\textsuperscript{4}Cognitive Neuroscience Laboratory, Graduate School of Natural Science and Technology, Okayama University, Okayama, Japan
linzl@szu.edu.cn

In the neuroimaging field of bilinguals, an important hypothesis – the assimilation/accommodation hypothesis - has been tested across alphabetic (e.g., English) and logographic (e.g., Chinese) languages that possess different properties in orthography and phonology. In the present study, we minimized the effects of orthography to test this hypothesis. Using fMRI, a group of native Japanese speakers who were late bilinguals in Chinese and a group of native Chinese speakers who were late bilinguals in Japanese were recruited to perform rhyming judgment tasks using both Japanese Kanji and Chinese characters, which share essentially consistent graphic forms of characters. We found that the Japanese participants recruited the bilateral inferior frontal gyrus (IFG) for the phonological processing of both Japanese Kanji and Chinese characters, whereas Chinese participants only recruited the bilateral IFG to process Japanese Kanji, but not Chinese characters. These results suggest that the Japanese and Chinese participants exhibited distinct, phonology-based assimilation/accommodation patterns. Specifically, Japanese participants showed an assimilation pattern, which suggests that the existing brain network for Japanese Kanji comprehension is recruited to process Chinese characters. Meanwhile, Chinese participants showed an accommodation pattern, which suggests that the existing brain network for Chinese characters is insufficient for processing the increased phonological valence of Japanese Kanji and that Japanese Kanji-related regions are thus provoked to process that language. Our findings shed new light on the understanding of how linguistic differences modulate cortical organization of language.

Unilateral peripheral facial paralysis (UPFP) is a form of facial nerve paralysis and clinically classified according to facial asymmetry. Prompt and precise assessment is crucial to the neural rehabilitation of UPFP.

For UPFP assessment, most of the existing assessment systems are subjective and empirical. Therefore, an objective assessment system will help clinical doctors to obtain a prompt and precise assessment. Distinguishing precisely between degrees of asymmetry is hard using pure pattern recognition methods. Thus, a novel objective assessment process based on convolutional neuronal networks is proposed in this paper that provides an end-to-end solution.

![Figure 1. (a) Conventional objective assessment process, (b) Deep assessment process](image)

As Figure 2(a) shows, the average misclassification rate to neighboring HB degrees is 10.54%, which is not particularly high. This illustrates that the problem of neighboring confusion could not be completely addressed if HB system is used as gold standard. This method could alleviate the problem and produced a classification accuracy of 91.25% for predicting the House-Brackmann degree on a given UPFP image dataset, such as shown in Table 1.

![Figure 2. Confusion matrices of HB degree classification. Values of matrices are in percentage.](image)

<table>
<thead>
<tr>
<th>Dataset</th>
<th>original</th>
<th>B</th>
<th>A</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Including degree</td>
<td>89.38%</td>
<td>86.88%</td>
<td>90.00%</td>
<td>91.25%</td>
</tr>
<tr>
<td>Excluding degree</td>
<td>81.91%</td>
<td>79.79%</td>
<td>82.98%</td>
<td>86.17%</td>
</tr>
</tbody>
</table>

Table 1. Classification accuracies of GoogLeNet models finetuned on original and augmented datasets

REFERENCES


Neural systems underlying lexical tone processing in Chinese reading

Veronica PY Kwok, & Li-Hai Tan

Center for Language and Brain, Shenzhen Institute of Neuroscience, Shenzhen 518057, China
veronkpy@sions.cn, tanlh@sions.cn

Past behavioral and neuroimaging studies have found the functional significance and neural substrates underlying syllable-level phonology in Chinese reading, but little is known concerning the contribution of lexical tone phonology to reading comprehension. In this study, we used fMRI to investigate the neural systems for lexical tone processing in Chinese reading. We found that the extraction of lexical tone information in printed scripts was subserved by a right lateralized fronto-parietal network, including bilateral inferior and middle frontal gyri, precentral gyri, cingulate gyri, supplementary motor area (SMA), right superior frontal gyrus, right precuneus, right supramarginal gyrus, and right middle temporal gyrus. In addition, we examined the functional connectivity among cortical regions in the right hemisphere. Seed-to-voxel analyses showed that the following three significant connections supported Chinese tone reading: (1) the right inferior frontal gyrus and right superior frontal gyrus/SMA were connected, (2) the right middle frontal gyrus was connected to the right inferior parietal lobule and right supramarginal gyrus, and (3) SMA was connected to bilateral cingulate gyri. These findings suggest that a right hemispheric network mediates lexical tone processing in visual word recognition. Our study is the first one to investigate the functional connectivity of lexical tone reading and thus, has provided insights to the neural circuitries engaged in the suprasegmental level of phonological processing in reading.

Keywords: fMRI, language, lexical tone, Chinese reading, suprasegmental phonology


An fMRI study of neural mechanisms underlying Semantic Processing in Reading

Fanlu Jia\textsuperscript{1,2}, Li Hai Tan\textsuperscript{1,2} & Wai Ting Siok\textsuperscript{1,3}

\textsuperscript{1} Center for Language and Brain, Shenzhen Institute of Neuroscience, Shenzhen 518057, China
\textsuperscript{2} Neuroimaging Laboratory, School of Biomedical Engineering, Shenzhen University Health Science Center, Shenzhen 518060, China
\textsuperscript{3} Neuroimaging Laboratory, Department of Linguistics, University of Hong Kong, Pokfulam Road, Hong Kong

\email{jiafl@sions.cn}
\email{tanlh@sions.cn}
\email{siok@hku.hk}

Previous neuroimaging studies have well-identified cortical substrates that are responsible for matured semantic processing. However, the human brain is a dynamic organ that experiences a sequence of salient changes throughout the life span, and thus, it is likely that changes of neural correlates are coincident with aging and accommodate successful semantic processing. Using functional MRI, we delineate the lifespan developmental changes in the neural substrates for semantic processing associated with age. A common left-lateralized neural system of the ventral inferior prefrontal gyrus, the posterior mid-superior temporal cortex, and the anterior superior temporal sulcus usually involved in semantic processes in reading was recruited across all participants. Whole brain-based correlation analysis indicated that age is associated with decreased activity in bilateral insula. ROI analysis revealed negatively correlations in left BA8 and right BA47. The activations of some important semantic brain regions remained unvaried across ages. Our findings demonstrate that neural circuits involved in semantic processes mature early and cortical activity is modulated by readers’ semantic skills.

Encoding of non-symbolic number information in human subcortex

Ke Zhou1,2, Zhentao Zuo3, Xue Ma1,2, Yuanyu Shi3

1 College of Psychology and Sociology, Shenzhen University, Shenzhen, China
2 Shenzhen Institute of Neuroscience, Shenzhen, China
3 Institute of Biophysics, Chinese Academy of Sciences, Beijing, China
Address: No.6 Yuexing 2nd Road, Nanshan District, Shenzhen, Guangdong Province, P.R. China, 518057
kzhou@szu.edu.cn

Humans and non-human primates exhibit remarkable ability to extract the number of elements from a visual display, usually referred to as non-symbolic number or numerosity. The “number sense” hypothesis proposes that numerosity is a basic visual property, similar to color, orientation, or contrast (Cicchini, Anobile, & Burr, 2016). Even newborn human infants as young as 48 h are able to discriminate abstract numerosity. And this preverbal sense of number in infancy predicts later mathematical abilities in early childhood. Recently, emerging evidence has shown that animals, without well-developed, or even in the absence of cerebral cortices (rat, bird, fish, newborn chick, honeybee, and spider), appear to possess the ability to evaluate relative quantities, suggesting that non-symbolic number sense may be evolutionarily conserved.

Numerous neuroimaging studies have showed that the parietal cortex, particularly the intraparietal sulcus (IPS), as well as some regions in frontal and occipital-parietal cortex, played a critical role in processing of numerical quantities (Harvey et al., 2013; Harvey & Dumoulin, 2017). However, the findings in animals and newborn infants alternatively implied that the numerosity processing may also rely on the more evolutionarily conserved regions (i.e., subcortical nuclei) of the human visual system. Thus, in the present study, to explore the possible contribution of subcortical structures to number processing in humans, we adopted an fMRI adaptation paradigm that allows us to directly infer the number selectivity in both cortical and subcortical regions.

Subjects were presented with the same number of 20 dots (adaptors) on the same locations in the visual field, which elicited strong adaptation effects (declined activity) in number-responsive brain regions. Occasionally, deviants with the different number of dots, ranged from 5 to 80, at the same location were shown. If a region is number-selective, presenting the deviant number should exhibit a recovery of fMRI responses, with an amount of activation inversely related to the number distance between adaptor and deviant. Consist with previous findings, strong number-selective adaptation effects were found in the bilateral IPS (Pinel et al., 2014). More importantly, a U-shaped activation curve, the classical signature of number sensitive coding, was also found in bilateral superior colliculus (SC). However, the representation of numerosity is coarser in SC as compared with IPS. Our preliminary fMRI results provide the initial neuroimaging evidence for the contributions of subcortical structures to non-symbolic number processing, which might serve as the ontogenetic and phylogenetical basis on which the more precise number encoding maybe be developed.

References

Acknowledgement This work was supported by the NSFC (31671133), Shenzhen Science and Technology Research Funding Program (JCYJ20170412164413575), Guangdong Pearl River Talents Plan Innovative and Entrepreneurial Team grant (2016ZT06S220).
The neural systems underlying phonological processing of Chinese characters

Kairou Guo\textsuperscript{1,2}

\textit{1 Neuroimaging Laboratory, School of Biomedical Engineering, Shenzhen University Health Science Center, Shenzhen 518060, China}
\textit{2 Center for Language and Brain, Shenzhen Institute of Neuroscience, Shenzhen 518057, China}
15822240185@163.com

A growing body of neuroimaging studies have shown that the neural system for Chinese character phonological processing is different from that of alphabetic languages because Chinese and alphabetic writing systems differ in important dimensions. Since most studies on this question recruited a small number of participants and no correction procedures were used in statistical analysis, they might suffer from the false positive rate problem. In this study, we performed two experiments to identify neural activation patterns for Chinese phonological processing: one was a meta-analysis using the activation likelihood estimation (ALE) method to summarize previous findings about phonological processing of Chinese characters and examined the neural activation patterns. In the second experiment, we performed a functional magnetic resonance imaging study, with a large sample size and stringent statistical threshold to see whether or not previous findings can be validated. Homophone judgment task was devised and sixty healthy adults participated in Experiment 2 Common activation patterns in the left middle frontal gyrus, left inferior frontal gyrus, superior frontal gyrus, left precentral gyrus, left insula, bilateral middle-inferior occipital gyrus, left lingual gyrus, left fusiform gyrus were seen for the two experiments. The results are consistent with the findings of previous studies investigating Chinese phonological processing and provide better understanding of the neural networks underlying phonological processing systems.