memory in unpolar and bipolar depression. Psychiatry Res 2011; 194: 378–384.
28. Takizawa R, Fukuda M, Kawasaki S et al. Neuroimaging-aided differential diagnosis of the depressive state. Neuroimage 2014; 85: 498–507.
29. Kubota Y, Toichi M, Shimizu M et al. Altered prefrontal lobe oxygenation in bipolar disorder: a study by near-infrared spectroscopy. Psychol Med 2009; 39: 1265–1275.
30. Kameyama M, Fukuda M, Yamagishi Y et al. Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. Neuroimage 2006; 29: 172–184.
31. Matsubara T, Matsuo K, Nakashima M et al. Prefrontal activation in response to emotional words in patients with bipolar disorder and major depressive disorder. Neuroimage 2014; 85: 489–497.
32. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct 2008; 213: 93–118.
33. Fleck DE, Eliassen JC, Durling M et al. Functional MRI of sustained attention in bipolar mania. Mol Psychiatry 2012; 17: 325–336.
34. Bermpohl F, Dalanay U, Kahnt T et al. A preliminary study of increased amygdala activation to positive affective stimuli in mania. Bipolar Disord 2009; 11: 70–75.
35. Cerullo MA, Fleck DE, Eliassen JC et al. A longitudinal functional connectivity analysis of the amygdala in bipolar I disorder across mood states. Bipolar Disord 2012; 14: 175–184.
36. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington, DC: APA, 2000.
37. Sheehan DV, Lecrubier Y, Sheehan KH et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59 (Suppl. 20): 22–33.
38. Matsuoka K, Uno M, Kasai K, Koyama K, Kim Y. Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. Psychiatry Clin Neurosci 2006; 60: 332–339.
39. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56–62.
40. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 133: 429–435.
41. Berk M, Ng F, Wang WV et al. The empirical redefinition of the psychometric criteria for remission in bipolar disorder. J Affect Disord 2008; 106: 153–158.
42. Kameyama M, Fukuda M, Uehara T, Mikuni M. Sex and age dependencies of cerebral blood volume changes during cognitive activation: a multichannel near-infrared spectroscopy study. Neuroimage 2004; 22: 1715–1721.
43. Suto T, Fukuda M, Ito M, Uehara T, Mikuni M. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. Biol Psychiatry 2004; 55: 501–511.
44. Takizawa R, Kasai K, Kawakubo Y et al. Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study. Schizophr Res 2008; 99: 250–262.
45. Koike S, Takizawa R, Nishimura Y et al. Different hemodynamic response patterns in the prefrontal cortical sub-regions according to the clinical stages of psychosis. Schizophr Res 2011; 132: 54–61.
46. Delpy DT, Cope M, van der Zee P, Arridge S, Wray S, Wyatt J. Estimation of optical pathlength through tissue from direct time of flight measurement. Phys Med Biol 1988; 33: 1433–1442.
47. Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H. Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Med Phys 1995; 22: 1997–2005.
48. Okamoto M, Dan H, Sakamoto K et al. Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. Neuroimage 2004; 21: 99–111.
49. Tsuzuki D, Jurcak V, Singh AK, Okamoto M, Watanabe E, Dan I. Virtual spatial registration of stand-alone fNIRS data to MNI space. Neuroimage 2007; 34: 1506–1518.
50. Singh AK, Okamoto M, Dan H, Jurcak V, Dan I. Spatial registration of multichannel multi-subject fNIRS data to MNI space without MRI. Neuroimage 2005; 27: 842–851.
51. Shattuck DW, Mirza M, Adisetiyo V et al. Construction of a 3D probabilistic atlas of human cortical structures. Neuroimage 2008; 39: 1064–1080.
52. Huppert TJ, Hoge RD, Diamond SG, Franceschini MA, Boas DA. A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans. Neuroimage 2006; 29: 368–382.
53. Strangman G, Culver JP, Thompson JH, Boas DA. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage 2002; 17: 719–731.
54. Singh AK, Dan I. Exploring the false discovery rate in multichannel NIRS. Neuroimage 2006; 33: 542–549.
55. Townsend JD, Bookheimer SY, Foland-Ross LC et al. Deficits in inferior frontal cortex activation in euthymic bipolar disorder patients during a response inhibition task. Bipolar Disord 2012; 14: 442–450.
56. Blumberg HP, Stern E, Ricketts S et al. Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. Am J Psychiatry 1999; 156: 1986–1988.
57. Ryan KA, Vederman AC, McFadden EM et al. Differential executive functioning performance by phase of bipolar disorder. Bipolar Disord 2012; 14: 527–536.
58. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci 2005; 9: 242–249.
59. Chen CH, Lennox B, Jacob R et al. Explicit and implicit facial affect recognition in manic and depressed states of bipolar disorder: a functional magnetic resonance imaging study. Biol Psychiatry 2006; 59: 31–39.
60. Allin MP, Marshall N, Schulze K et al. A functional MRI study of verbal fluency in adults with bipolar disorder and their unaffected relatives. Psychol Med 2010; 40: 2025–2035.
61. Curtis VA, Thompson JM, Seal ML et al. The nature of abnormal language processing in euthymic bipolar I disorder: evidence for a relationship between task demand and prefrontal function. Bipolar Disord 2007; 9: 358–369.
62. Hulvershorn LA, Karne H, Gunn AD et al. Neural activation during facial emotion processing in unmedicated bipolar depression, euthymia, and mania. Biol Psychiatry 2012; 71: 603–610.
63. Strakowski SM, Adler CM, Cerullo M et al. Magnetic resonance imaging brain activation in first-episode bipolar mania during a response inhibition task. Early Interv Psychiatry 2008; 2: 225–233.
64. Fuster JM. The Prefrontal Cortex, 4th edn. London: Academic Press, 2008.

65. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. Cereb Cortex 2006; 16: 916–928.
66. Sawa M, Yamashita H, Fujimaki K, Okada G, Takahashi T, Yamawaki S. Negative correlation between affective symptoms and prefrontal activation during a verbal fluency task: a near-infrared spectroscopy study. Neuropsychobiology 2013; 67: 103–110.
67. Phillips BD, Gopalakrishnan G, Gohh R, Hennessey JV. Lithium toxicity precipitated by profound hypothyroidism. Thyroid 2008; 18: 651–654.
68. Michael N, Erfurth A, Ohrmann P et al. Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorsolateral prefrontal cortex. Psychopharmacology 2003; 168: 344–346.
69. Nonaka S, Hough CJ, Chuang DM. Chronic lithium treatment robustly protects neurons in the central nervous system against excitotoxicity by inhibiting N-methyl-D-aspartate receptor-mediated calcium influx. Proc Natl Acad Sci USA 1998; 95: 2642–2647.
70. Silverstone PH, Bell EC, Willson MC, Dave S, Wilman AH. Lithium alters brain activation in bipolar disorder in a task- and state-dependent manner: an fMRI study. Ann Gen Psychiatry 2005; 4: 14.
71. Maina G, Albert U, Bellodi L et al. Health-related quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes. J Clin Psychiatry 2007; 68: 207–212.
72. Li CT, Hsieh JC, Wang SJ et al. Differential relations between fronto-limbic metabolism and executive function in patients with remitted bipolar I and bipolar II disorder. Bipolar Disord 2012; 14: 831–842.
73. Hafeman DM, Chang KD, Garrett AS, Sanders EM, Phillips ML. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. Bipolar Disord 2012; 14: 375–410.

analgesics, hormone therapy, anticonvulsants and α-lipoic acid.[5] Considering the high incidence of psychiatric features, it seemed that the psychiatric interventions for BMS were underestimated with only few randomized control trials focusing on treating BMS with psychotropic agents.

In our opinion, BMS may include the disturbance of both the physiological and psychological systems. Anxiety, depression, pain disorder, hypochondriasis as well as delusional disorder should be considered for BMS. Thus, when clinicians see BMS patients, besides arranging a detailed physical examination, the psychological aspects should also be considered and psychiatric consultation may be needed. In this way, there will be a more comprehensive consideration for BMS.

There are no potential conflicts of interest and no financial support, including drug stores, for any authors. There is also no grant support for this report. At the same time, we have no special circumstances, vested interests, or sources of funding to disclose.

REFERENCES

1. Bergdahl J, Anneroth G. Burning mouth syndrome: Literature review and model for research and management. *J. Oral Pathol. Med.* 1993; 22: 433–438.
2. Basker RM, Sturdee DW, Davenport JC. Patients with burning mouths. A clinical investigation of causative factors, including the climacteric and diabetes. *Br. Dent. J.* 1978; 145: 9–16.
3. Eli I, Baht R, Littner MM, Kleinhauz M. Detection of psychopathologic trends in glossodynia patients. *Psychosom. Med.* 1994; 56: 389–394.
4. Grushka M, Sessle BJ. Burning mouth syndrome. *Dent. Clin. North Am.* 1991; 35: 171–184.
5. Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome. *Cochrane Database Syst. Rev.* 2005; (1): CD002779.

Yao-Tung Lee, MD,[1] Liang-Yu Chen, MD[2] and Hsin-Chien Lee, MD, MPH[3]
[1]*Department of Psychiatry, Shuang-Ho Hospital, Taipei Medical University, New Taipei City,* [2]*Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, and* [3]*Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
Email: rain7244@gmail.com
Received 18 April 2014; revised 25 June 2014; accepted 25 July 2014.

Psychological symptom and social functioning subscales of the modified Global Assessment of Functioning scale: Reliability and validity of the Japanese version

doi:10.1111/pcn.12250

THE GLOBAL ASSESSMENT of Functioning (GAF) scale and the Social and Occupational Functioning Scale (SOFAS) easily and quickly evaluate overall function using a single continuous value with anchor points, and they are widely used in both clinical and research settings.[1] These scales, however, are subject to variability and can be influenced by the rater's level of education and experience and training with the scale, as well as the quality and quantity of the patient's clinical information. Thus, the modified GAF (mGAF-original) scale was developed to improve the reliability and validity of the original GAF scale.[2] We obtained the author's permission to translate the mGAF-original scale into Japanese and to make new scales using the items and anchor points in it. Subsequently, we developed the Japanese version of the mGAF-original scale as well as the psychological symptom (mGAF-S) and social functioning (mGAF-F) subscales by splitting the items and anchor points of the mGAF-original scale. We used the lower value of the mGAF-S and mGAF-F scores for the mGAF score in accordance with instructions of the original GAF evaluation.[1] We tested inter-rater reliability and concurrent validity for the new subscales.

Developed scales, and detailed methods and results are shown in Supporting information. To test inter-rater reliability, five professionals administered the original and modified GAF scales to five patients with schizophrenia. To test concurrent validity, 10 professionals administered the original and modified GAF scales, and the Positive and Negative Syndrome Scale (PANSS) to 31 patients with schizophrenia. Participants gave written informed consent.

The intra-class correlation coefficients (ICC) of the mGAF-original, mGAF-S, mGAF-F, and mGAF scales were 0.94, 0.8, 0.96, and 0.96, respectively. The mGAF-original score was significantly correlated with the GAF score ($r = 0.91$, $P < 0.001$), and the mGAF score was significantly correlated with the GAF and mGAF-original scores (mGAF and GAF: $r = 0.89$, $P < 0.001$; mGAF and mGAF-original: $r = 0.97$, $P < 0.001$). The mGAF-S score was significantly correlated with the PANSS positive ($r = -0.54$, $P = 0.002$), negative ($r = -0.50$, $P = 0.004$), general psychopathology ($r = -0.59$, $P < 0.001$), and total scores ($r = -0.61$, $P < 0.001$). The mGAF-F score significantly correlated with the SOFAS score ($r = 0.88$, $P < 0.001$).

Our study showed excellent inter-rater reliability and concurrent validity of the Japanese versions of the mGAF-original, mGAF-S, mGAF-F, and mGAF scales. These modified versions of the GAF scale may be easier and more appropriate when separately evaluating current psychological symptoms and social functioning than the original GAF and SOFAS scales.

The Japanese version of the mGAF-original, mGAF-S, mGAF-F, and mGAF scales are available within research settings for Japanese participants, and readers can contact the corresponding author (http://npsy.umin.jp/indicator.html) if they would like to use them.

REFERENCES

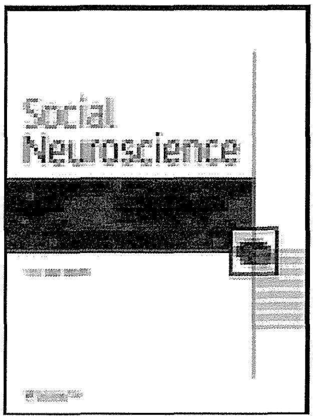
1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4rd edn. Text Revised. American Psychiatric Association, Washington, DC, 1994.
2. Hall RC. Global assessment of functioning. A modified scale. *Psychosomatics* 1995; 36: 267–275.

Satoshi Eguchi, MSc,[1] Shinsuke Koike, MD, PhD,[2,3]
Motomu Suga, MD, PhD,[1] Ryu Takizawa, MD, PhD[2] and
Kiyoto Kasai, MD, PhD[2]
Departments of [1]Rehabilitation and [2]Neuropsychiatry, Graduate School of Medicine, and [3]Office for Mental Health Support, Division for Counseling and Support, The University of Tokyo, Tokyo, Japan
Email: skoike-tky@umin.ac.jp
Received 29 May 2014; revised 20 October 2014; accepted 29 October 2014.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Modified Global Assessment of Functioning (GAF) scale.
Appendix S2. Detailed method.



Social Neuroscience
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/psns20

Using social epidemiology and neuroscience to explore the relationship between job stress and frontotemporal cortex activity among workers

Shingo Kawasaki[ab], Yukika Nishimura[a], Ryu Takizawa[ai], Shinsuke Koike[ac], Akihide Kinoshita[a], Yoshihiro Satomura[a], Eisuke Sakakibara[a], Hanako Sakurada[a], Mika Yamagishi[a], Fumichika Nishimura[a], Akane Yoshikawa[a], Aya Inai[d], Masaki Nishioka[ae], Yosuke Eriguchi[f], Chihiro Kakiuchi[a], Tsuyoshi Araki[f], Chiemi Kan[g], Maki Umeda[g], Akihito Shimazu[g], Hideki Hashimoto[h], Norito Kawakami[g] & Kiyoto Kasai[a]

[a] Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[b] Hitachi Medical Corporation, Application Development Office, Chiba, Japan

[c] Office for Mental Health Support, Division for Counseling and Support, The University of Tokyo, Tokyo, Japan

[d] Department of Child Neuropsychiatry, The University of Tokyo Graduate School of Medicine, Tokyo, Japan

[e] Department of Molecular Psychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[f] Department of Youth Mental Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[g] Department of Mental Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[h] Department of Health Economics & Epidemiology Research, School of Public Health, The University of Tokyo, Tokyo, Japan

[i] MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

Published online: 12 Jan 2015.

To cite this article: Shingo Kawasaki, Yukika Nishimura, Ryu Takizawa, Shinsuke Koike, Akihide Kinoshita, Yoshihiro Satomura, Eisuke Sakakibara, Hanako Sakurada, Mika Yamagishi, Fumichika Nishimura, Akane Yoshikawa, Aya Inai, Masaki Nishioka, Yosuke Eriguchi, Chihiro Kakiuchi, Tsuyoshi Araki, Chiemi Kan, Maki Umeda, Akihito Shimazu, Hideki Hashimoto, Norito Kawakami & Kiyoto Kasai (2015): Using social epidemiology and neuroscience to explore the relationship between job stress and frontotemporal cortex activity among workers, Social Neuroscience, DOI: 10.1080/17470919.2014.997370

To link to this article: http://dx.doi.org/10.1080/17470919.2014.997370

SOCIAL NEUROSCIENCE, 2015
http://dx.doi.org/10.1080/17470919.2014.997370

Using social epidemiology and neuroscience to explore the relationship between job stress and frontotemporal cortex activity among workers

Shingo Kawasaki[1,2], Yukika Nishimura[1], Ryu Takizawa[1,9], Shinsuke Koike[1,3], Akihide Kinoshita[1], Yoshihiro Satomura[1], Eisuke Sakakibara[1], Hanako Sakurada[1], Mika Yamagishi[1], Fumichika Nishimura[1], Akane Yoshikawa[1], Aya Inai[4], Masaki Nishioka[1,5], Yosuke Eriguchi[6], Chihiro Kakiuchi[1], Tsuyoshi Araki[6], Chiemi Kan[7], Maki Umeda[7], Akihito Shimazu[7], Hideki Hashimoto[8], Norito Kawakami[7], and Kiyoto Kasai[1]

[1]Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Hitachi Medical Corporation, Application Development Office, Chiba, Japan
[3]Office for Mental Health Support, Division for Counseling and Support, The University of Tokyo, Tokyo, Japan
[4]Department of Child Neuropsychiatry, The University of Tokyo Graduate School of Medicine, Tokyo, Japan
[5]Department of Molecular Psychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[6]Department of Youth Mental Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[7]Department of Mental Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[8]Department of Health Economics & Epidemiology Research, School of Public Health, The University of Tokyo, Tokyo, Japan

Correspondence should be addressed to: Kiyoto Kasai, Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan. E-mail: kasaik-tky@umin.net

Please note the following disclosures of potential conflicts of interest regarding the financial aspects of the present study. Kiyoto Kasai of the University of Tokyo has an interest in the submitted work. The University of Tokyo has an official contract with Hitachi Medical Corporation for a collaborative study on the clinical application of NIRS. In addition, Hitachi Medical Corporation provided a project grant (JPY300,000 per year) toward this study. Shingo Kawasaki is employed by Hitachi Medical Corporation, and is also a contract researcher at the University of Tokyo. Other authors of this manuscript have neither financial relationships with any organization that could have an interest in the submitted work, nor engage in other relationships or activities that could influence the submitted work.

This study was conducted as an interdisciplinary collaboration between the two Grants-in-Aid for Scientific Research on Innovative Areas by MEXT, Japan: The "Elucidation of social stratification mechanism and control over health inequality in contemporary Japan: New interdisciplinary area of social and health sciences" project [grant number 21119003 to NK and TA], and "Adolescent Mind & Self-Regulation" project [grant number 23118001], [grant number 23118004] to KK. This study was also supported by grants from the Ministry of Health, Labour and Welfare [Health and Labour Science Research Grants for Comprehensive Research on Disability Health and Welfare, H23-seishin-ippan-002 and H25-seishin-ippan-002 to RT, YN, ES, and KK]; the JSPS/MEXT [Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network to KK), 23791309 and 26860914 to RT]; the Intramural Research Grant [23-10 and 26-3] for Neurological and Psychiatric Disorders of NCNP (to RT, YN, ES, and KK).

[9]MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

Mental health problems, such as depression, are increasingly common among workers. Job-related stresses, including psychological demands and a lack of discretion in controlling one's own work environment, are important causal factors. However, the mechanisms through which job-related stress may affect brain function remain unknown. We sought to identify the relationship between job-related stress and frontotemporal cortex activation using near-infrared spectroscopy. Seventy-nine (45 females, 34 males) Japanese employees, aged 26–51 years, were recruited from respondents to the Japanese Study of Stratification, Health, Income, and Neighborhood survey. Job-related stress was measured using the Japanese version of Job Content Questionnaire, which can index "job demand" and "job control". We found a significant correlation between higher "job demand" and smaller oxygenated hemoglobin [oxy-Hb] changes in the left dorsolateral prefrontal cortex in female (r = −.54 to −.44). Significant correlations between higher "job control" and greater [oxy-Hb] changes in the right temporal cortex were observed among male, and in the combined sample (r = .46–.64). This initial cross-sectional observation suggests that elevated job-related stress is related to decrease frontotemporal cortex activation among workers. Integrating social epidemiology and neuroscience may be a powerful strategy for understanding how individuals' brain functions may mediate between the job-related stress or psychosocial work characteristics and public mental health.

Keywords: Job-related stress; Job demand-control model; Frontotemporal cortex activation; Near-infrared spectroscopy; Social epidemiolog.

Mental health problems in occupational environments, such as major depression and other stress-related disorders, are a serious public health issue (Benach, Muntaner, Santana, & the Employment Conditions Knowledge Network (EMCONET), 2007). Social epidemiology has been trying to disentangle how social stratification may affect work environment (Berkman & Kawachi, 2000), and neuroscientists have sought to clarify how stress affects brain function in both animal models (Holmes & Wellman, 2009) and humans (Arnsten, 2009; McEwen & Morrison, 2013), albeit under largely experimental conditions.

According to social epidemiology and psychology, job-related stress is an important component of social determinants of health in the occupational environment (S. Stansfeld & Candy, 2006). The Job Demand-Control (JDC) model, proposed by Karasek, Baker, Marxer, Ahlbom, and Theorell (1981), is a well-established model of the relationship between job stress and health. The JDC model focuses on the workload ("job demand") and degree of discretion exercised in relation to work ("job control"). In short, job demand refers to a combination of work stressors, including quantitative workload and one's own role in workplace, while job control is defined as one's skill level and work-decision authority. In the JDC model, workers with high job demand and low job control may be theoretically regarded as being the group under the highest strain. These individuals exhibit sensitive reactions to psychological stress, and a state of high strain negative impacts their health; their conditions include cardiovascular disease (Eller et al., 2009; Kivimaki et al., 2012), hypertension (Ohlin, Berglund, Rosvall, & Nilsson, 2007), and mental health problems, such as depressive symptoms and major depressive disorder (Bonde, 2008; Cropley, Steptoe, & Joekes, 1999; De Lange, Taris, Kompier, Houtman, & Bongers, 2003; Netterstrom et al., 2008; S. Stansfeld & Candy, 2006; S. A. Stansfeld, Fuhrer, Shipley, & Marmot, 1999; Wang, Schmitz, Dewa, & Stansfeld, 2009).

An epidemiological study showed that gender differences appeared to be larger for job control, with male perceiving higher control at work than female (De Smet et al., 2005; Li, Yang, & Cho, 2006). Other epidemiological study showed that job strain lead to higher impact for female than for male (Vanagas, Bihari-Axelsson, & Vanagiene, 2004). These studies showed that the JCD model may have different effect between male and female.

Neuroscience research has suggested that psychological stress has an influence on prefrontal cortex function in animals and humans (Holmes & Wellman, 2009; McEwen & Morrison, 2013). When an individual is exposed to psychological stress, the amygdala activates stress pathways in the brainstem and hypothalamus which impair the higher-order functions of the prefrontal cortex, such as working memory and attention regulation (Arnsten, 2009). Prefrontal impairments manifest in various psychiatric disorders, such as major depression and stress-related disorders (Arnsten, 2007; Drevets, 2000). These converging results have suggested that stress induces prefrontal dysfunction. In addition, it is common knowledge that gender influences on brain structure and function (Cahill, 2006). These converging results have suggested that stress induces prefrontal dysfunction by gender in a different way.

It is possible to integrate social epidemiology and neuroscience to clarify the mechanism that underpins the social determinants of health. To do so, we must first elucidate the relationship between job-related stress and brain function. Previous studies have demonstrated the possible effects of chronic stress on prefrontal function. Liston, McEwen, and Casey (2009) reported that students exposed to 1 month of psychological stress associated with academic examinations showed impaired prefrontal function; however, this impairment was largely reversible. Other studies examined the brain response to an individual's temporary exposure to psychological stress (Qin, Hermans, Van Marle, Luo, & Fernandez, 2009; Wang et al., 2007; Yang, Zhou, Gong, Luo, & Lu, 2009; Yang et al., 2007). Ohira et al. (2011) measured $[^{15}O]$ H_2O using positron emission tomography (PET) imaging during the reversal-learning task in 20 healthy men. Their results showed that participants with high job stress exhibited decreased activity in the anterior caudate, orbitofrontal cortex, ventrolateral prefrontal cortex, insula, and midbrain, all of which are involved in goal-directed action. To our knowledge, however, no study has investigated the relationship between job-related stress and brain function in a relatively large, unbiased sample of workers, such as those recruited from a population-based social epidemiological survey.

Obtaining neuroimaging data from a large cohort is challenging. Multi-channel near-infrared spectroscopy (NIRS) is a functional imaging system that enables noninvasive, less-constrained measurement of the spatiotemporal characteristics of cerebral function. Thus, NIRS, compared with other neuroimaging techniques, such as PET and functional magnetic resonance imaging (fMRI), is appropriate for use in large-scale surveys, such as community-based cohort studies. Recently, NIRS studies have reported that subjective emotions, including anxiety (Takizawa, Nishimura, Yamasue, & Kasai, 2013), subjective fatigue (Suda et al., 2009), and apathy (Sawa et al., 2013), were associated with frontotemporal cortex activation in healthy adults. Additionally, NIRS studies reported that patients with major depressive disorder showed lower-than-healthy frontotemporal cortex activation during a cognitive task (Suto, Fukuda, Ito, Uehara, & Mikuni, 2004; Takizawa et al., 2014). Another NIRS study reported that individuals who were more depressed exhibited lower frontotemporal cortex activation among a sample of individuals with major depressive disorder (Noda et al., 2012). Considering the previous studies, decreased prefrontal cortex activation during the cognitive task is estimated to indicate the prefrontal cortex dysfunction. These findings suggest that NIRS may show the impact of psychological stress on brain activity.

In the present study, we investigated the effects of job stress on brain function, as detected by NIRS during a verbal fluency task (VFT), in a large sample of workers recruited from a population-based survey of social-stratification determinants of health. We hypothesized that higher "job demand" and lower "job control" would induce frontotemporal cortex dysfunction, and this effect would differ between men and women.

MATERIALS AND METHODS

Participants

A total of 79 (45 females, 34 males) Japanese employees, aged 26–51 years, were invited to participate in the study (Table 1). Participants were recruited from two of the four cities in the metropolitan region of Tokyo sampled in the Japanese Study of Stratification, Health, Income, and Neighborhood (J-SHINE) survey (Takada, Kondo, & Hashimoto, 2014). In J-SHINE, adult community inhabitants, aged 25–50 years, were probabilistically selected from the residential registry in each of four municipalities (two in Tokyo metropolitan area and two in neighboring prefectures). All participants were unmarried native Japanese speakers. The exclusion criterion for this group was a history of neurological or psychiatric disease. To rule out any neurological and psychiatric disorder, trained investigator interviewed all participants using questionnaire information written by the participants. This study was approved by the Research Ethics Committee of the University of Tokyo Hospital (approval No. 630-7, 3361). Following a thorough explanation of the study requirements and procedures, all participants provided written informed consent, in accordance with the Declaration of Helsinki.

Measures

Job-related stress was measured using the Japanese version of Job Content Questionnaire (JCQ) (Kawakami & Fujigaki, 1996). The JCQ is a self-reported assessment based on the JDC model (Karesek & Theorell, 1990). The JCQ is the 22-item self-report scale that can measure job demand and job control, as defined according to the JDC model. Job demand comprises five elements (working fast, working hard, demand for extra work, insufficient time to work, and conflicting demands). Job control was defined as the sum of two subscales: (1) skill

TABLE 1
Participants' demographic and clinical characteristics

	Total (female + male)		Female		Male		Gender difference
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p-Value*
N	79		45		34		
Age, years	33.7	6.0	33.8	5.9	33.6	6.2	0.865
Education, years	15.2	2.0	15.2	1.9	15.3	2.2	0.852
Annual personal income, million Yen	3.4	1.6	3.3	1.9	3.5	1.6	0.624
Estimated IQ	107.6	9.0	106.1	9.4	109.6	8.3	0.082
Sleepiness	2.0	0.9	1.9	0.9	2.2	0.9	0.069
Task performance	15.7	4.4	15.6	3.9	16.0	5.1	0.684
CES-D	9.1	6.1	8.6	5.9	9.9	6.3	0.349
Job Content Questionnaire							
Job demand	32.3	6.3	31.0	6.1	34.0	7.9	0.062
Job control	67.0	11.2	65.6	11.2	68.8	11.2	0.215
Job strain	1.00	0.33	0.98	0.33	1.02	0.33	0.637

Notes: IQ: intelligence quotient; CES-D: Center for Epidemiologic Studies Depression Scale; Job strain: job demand/job control × 2.

discretion, measured by four elements (the continuous need to acquire new knowledge, skill requirement, requirement for creativity, and repetitiveness); and [2] decision authority, measured by two elements (freedom to make decisions and choice in the approach to work). Under the JDC model, job strain was defined as the ratio between job demand and job control (Job demand/Job control × 2). Information regarding participant age, years of education, and annual personal income was also obtained. Furthermore, an estimate of each participant's intelligence quotient (IQ) was obtained through the 25-item Japanese version of the National Adult Reading Test (JART25) (Matsuoka, Uno, Kasai, Koyama, & Kim, 2006). The Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D) was also administered to measure participants' depression levels (Shima, Shikano, Kitamura, & Asai, 1985). Each participant's sleepiness was evaluated using the Stanford Sleepiness Scale (Hoddes, Dement, & Zarcone, 1971).

Verbal fluency task

The cognitive activation task was a modified letter version of the VFT employed for the NIRS measurements. Each participant was seated in a comfortable chair in a room during the daytime with eyes open throughout the measurement. Participants performed a VFT consisting of a 30-s pre-task baseline period, a 60-s task period, and a 70-s post-task baseline period (Takizawa et al., 2014).

Briefly, for the 60-s task period, the participant was instructed to verbally generate as many words as possible that begin with a given initial Japanese syllable. The task period was split into three sub-periods; participants were required to generate words using three syllables (first, /a/, /to/, or /na/; second, /ki/, /se/, or /i/; third, /ha/, /o/, or /ta/). These syllables changed every 20 s to prevent participants from being silent. In the 30-s pre-task and 70-s post-task periods, the participants were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ (the Japanese counterparts of a, b, c, d, and e in English). We recorded the total number of correct words generated by each participant during the VFT period.

NIRS measurement

Oxygenated hemoglobin ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) concentration changes were measured using 52-channel NIRS (ETG-4000, Hitachi Medical Corporation, Japan) to measure the absorption of two wavelengths of near-infrared light (695 and 830 nm). In addition, [oxy-Hb] and [deoxy-Hb] were calculated according to the modified Beer–Lambert law (Delpy et al., 1988). The distance between the pair of emission and detection probes was set at 30 mm; the NIRS machine measured [Hb] at the midpoints between the probes at depths of 20–30 mm from the scalp; that is, the surface of the cerebral cortex (Toronov et al., 2001). We defined the midpoints between the probes as one "channel." The NIRS probes were placed on a participant's frontotemporal region with the mid-column of the probe located over Fpz in accordance with the international 10/20 system used in electroencephalography. The probes measured [Hb] changes at 52 measurement points arranged in a 6 × 30-cm area. The arrangement of probes measured [Hb] from the bilateral prefrontal cortical areas (e.g., frontopolar (FP; approximately corresponding to Brodmann's area (BA) 10), dorsolateral (DL; BA 9, 46), ventrolateral (VL; BA 44, 45, 47)), and superior temporal cortical surface regions—an approach supported by a multi-subject study of anatomical craniocerebral correction via the international 10/20 system (Okamoto et al., 2004). The estimated cortical regions were localized at each channel using a virtual registration method available at Jichi Medical University (Tsuzuki et al., 2007).

The absorption of near-infrared light was measured with a time resolution of 0.1 s. The data were analyzed using the "integral mode": the pre-task baseline was determined as the mean across the last 10 s of the 30 s pre-task period; the post-task baseline was determined as the mean across the last 10 s of the 70 s post-task period. Linear fitting was applied to the data between these two baselines, as described in previous studies (Kameyama et al., 2006; Suto et al., 2004). The moving average method (5 s moving average window) was used to exclude short-term motion artifacts in the analyzed data. Even with these artifact-rejection procedures, visible artifact waveforms remained. Thus, we used a computer program that rejected a channel when artifact waveforms were visible (Takizawa et al., 2014).

Statistical analysis

First, the mean [oxy-Hb] and [deoxy-Hb] changes during the VFT period were compared between male and female participants for each channel using Student's t-tests. Then, Pearson's correlation coefficients were calculated for each channel in order to assess the relationship between the mean [oxy-Hb] and [deoxy-Hb] changes and JCQ characteristics (job demand, job control, and job strain). Since we performed 52 t-tests, we also applied the false discovery rate (FDR) correction for multiple comparisons. We specified a maximum FDR value of 0.05 to ensure a false -positive rate no more than 5% on average (Singh & Dan, 2006). For the channels with significant correlation between mean [oxy-Hb] change and JCQ scores in each gender group, we performed three hierarchical multiple regression analysis to confirm the relationship between mean [oxy-Hb] changes and demographic characters (gender, age, estimated IQ, CES-D, sleepiness, task performance, and JCQ scores). We used mean [oxy-Hb] changes during the VFT in each channel as a dependent variable and demographic characters as independent factors. In the first step (Step1), the JCQ score and gender were entered. Next step (Step2), interaction effect (the JCQ score × gender) was added as a dependent variable. Final step (Step3), six demographic characters (age, estimated IQ, CES-D, sleepiness, task performance, and remain JCQ score) were added further dependent variables in a stepwise manner (entry: p = .05; and removal: p = .10).

All statistical analyses were performed using SPSS 19.0 J (IBM Inc., Armonk, NY, USA) and MATLAB R2011 (MathWorks Inc., Natick, MA, USA) software.

RESULTS

Demographic characteristics

There were no significant differences between male and female participants with regard to mean age, years of education, annual personal income, estimated IQ, sleepiness, task performance, CES-D, and JCQ scores (Table 1). No significant correlation was observed between job demand and job control in the total (male plus female) sample (r = .08, p = .48). We found a positive correlation between years of education and job control in the total sample (r = .25, p = .03). No significant correlations were found in any other combinations of the variables.

Difference between male and female in NIRS signal

No significant difference was found in mean [oxy-Hb] changes during the VFT period between male and female participants for any channels (FDR-corrected $p > .05$). The mean [deoxy-Hb] change was significantly lower for female than male participants at one channel (ch1: FDR-corrected p = .0009), located approximately in the right-primary somatosensory cortex.

Correlation between JCQ score and NIRS signal

Figure 1 depicts the relationship between job demand and mean [oxy-Hb] change during the VFT period in the total sample. Among female participants, higher job demand was associated with lower [oxy-Hb] during the VFT period at seven channels (ch6: $r = -.44$, ch18: $r = -.42$, ch21: $r = -.44$, ch28: $r = -.42$, ch39: $r = -.51$, ch48: $r = -.54$, ch49: $r = -0.51$; FDR-corrected p = .0004–.0052), located approximately in the left-middle frontal and left-inferior frontal regions. There was no significant correlation between job

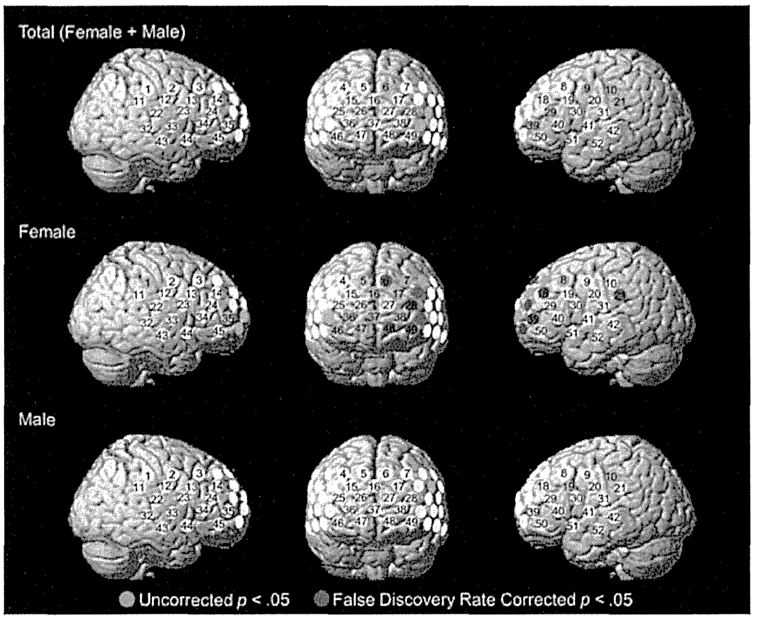


Figure 1. The relationship between job demand and mean [oxy-Hb] change during the VFT period using Pearson's correlation. Brain area in red corresponds to the NIRS channels that showed a significant correlation (FDR-corrected $p < .05$), and brain area in pink corresponds to the NIRS channels that showed a significant correlation (uncorrected $p < .05$).

demand and mean [oxy-Hb] change (FDR-corrected $p > .05$) for the total or male sample. Furthermore, there was no significant correlation between job demand and mean [deoxy-Hb] change during the VFT period for the total, male, or female sample (FDR-corrected $p > .05$).

Figure 2 shows the relationship between job control and mean [oxy-Hb] change. Lower job control was associated with decreased [oxy-Hb] changes during the VFT for the total sample at two channels (ch43: $r = .51$, ch44: $r = .46$; FDR-corrected $p = .0001–.0006$), located approximately in the right-middle temporal region. Similarly, a significant positive correlation between job control and mean [oxy-Hb] changes during the VFT period was found at one channel (ch43: $r = .64$; FDR-corrected $p = 0.0007$) among male participants, located approximately in the right-middle temporal cortex. No significant correlations were found between job control and mean [oxy-Hb] changes (FDR-corrected $p > .05$) among female participants or between job control and mean [deoxy-Hb] change during the VFT for the total, male, or female sample (FDR-corrected $p > .05$).

Job strain was not significantly correlated with mean [oxy-Hb] and [deoxy-Hb] changes for the total, male, or female sample (FDR-corrected $p > .05$).

Table 2 showed that the results of the hierarchical multiple regression analysis. For job demand score, the following two steps showed that job demand and gender have meaningful relationship of mean [oxy-Hb] change independently, without the interaction effect between job demand and gender in five channels (ch6, 18, 21, 28, and 39, Figure 3(a)) localized in the left dorsolateral prefrontal cortex and the left superior temporal cortex. In contrast, the interaction effect between job demand and gender has meaningful relationship of mean [oxy-Hb] change in two channels (ch48 and 49, Figure 3(b)) localized in the left frontopolar cortex. The final step (Step3) showed that significant contributions were found for estimated IQ in channel 21, and task performance in channels 28 and 39. For job control score, the following two steps showed that job control have meaningful relationship of mean [oxy-Hb] change without effects of gender or the interaction between job control and gender in two channels (ch43 and 44, Figure 3(c)) localized in the right middle temporal cortex. The final step (Step3) showed that no significant additional relationship of mean [oxy-Hb] change in channels 43 and 44 and demographic variables.

Other correlational analyses

We found a negative correlation between years of education and mean [oxy-Hb] changes during the

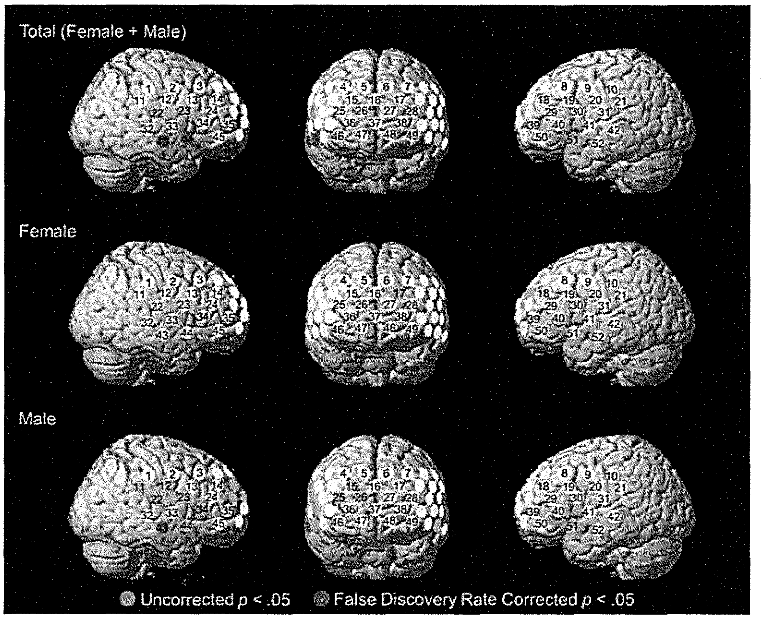


Figure 2. The relationship between job control and mean [oxy-Hb] change during the VFT period using Pearson's correlation. Brain area in red corresponds to the NIRS channels that showed a significant correlation (FDR-corrected $p < .05$), and brain area in pink corresponds to the NIRS channels that showed a significant correlation (uncorrected $p < .05$).

TABLE 2
Results of the hierarchical multiple regression analysis

JCQ	*Channel*	*Step**	ΔR^2	ΔF	*df*	*p-Value*
Job demand	Left dorsolateral prefrontal cortex					
	6	1	0.142	5.948	2.72	0.004
		2	0.021	1.760	1.71	0.189
	18	1	0.122	5.001	2.72	0.009
		2	0.004	0.321	1.71	0.573
	28	1	0.098	4.013	2.74	0.022
		2	0.004	0.323	1.73	0.572
		3 (task performance)	0.073	6.336	1.72	0.014
	39	1	0.130	5.245	2.70	0.008
		2	0.024	1.959	1.69	0.166
		3 (task performance)	0.047	4.018	1.68	0.049
	48	1	0.038	1.232	2.63	0.299
		2	0.075	5.268	1.62	0.025
	49	1	0.076	2.815	2.68	0.067
		2	0.052	3.973	1.67	0.050
	Left superior temporal cortex					
	21	1	0.196	7.908	2.65	0.001
		2	0.003	0.255	1.64	0.616
		3 (estimated IQ)	0.048	4.019	1.63	0.049
Job control	Right middle temporal cortex					
	43	1	0.260	8.661	2.49	0.001
		2	0.053	3.696	1.48	0.061
	44	1	0.211	6.549	2.49	0.003
		2	0.030	1.893	1.48	0.175

Notes: *Entered independent variables; Step1: the JCQ score and gender; Step2: interaction effect (the JCQ score × gender); Step3 in a stepwise manner: age, estimated IQ, CES-D, sleepiness, task performance and remain JCQ score.

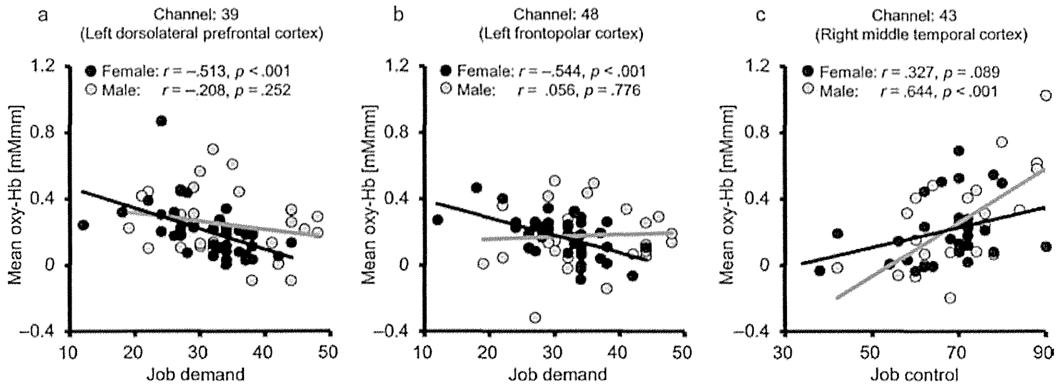


Figure 3. (a) Scatterplots for correlations between job demand and mean [oxy-Hb] change during the VFT period at channel 39 (left dorsolateral prefrontal cortex) in female (black) and male (gray). (b) Scatterplots for correlations between job demand and mean [oxy-Hb] change during the VFT period at channel 48 (left frontopolar cortex) in female (black) and male (gray). (c) Scatterplots for correlations between job control and mean [oxy-Hb] change during the VFT period at channel 43 (right middle temporal cortex) in female (black) and male (gray).

VFT period in the total sample (ch30: $r = -.56$; FDR-corrected $p = .0005$) and the female sample (ch2: $r = -.55$; FDR-corrected $p = .0006$). No significant correlations were found between any other variables and mean [oxy-Hb] or [deoxy-Hb] changes during the VFT period in the total, male, or female sample.

DISCUSSION

As hypothesized, our study showed a significant association between job stress and frontotemporal cortex activation. Higher job demand was correlated with decreased activation in the left-middle and inferior frontal regions among females, while lower job control was associated with decreased brain activation in the right-middle temporal region in both the total and male samples. To the best of our knowledge, this is the first study that integrates social epidemiology and neuroscience to depict the association between job stress and brain activity in a relatively large, unbiased sample of workers.

The relationship between job demand and frontotemporal cortex activity

In this study, higher job demand was associated with lower activation in the left dorsolateral prefrontal cortex among female participants. Several studies have found the association between high job demand and depressive symptoms (Broadbent, 1985; Bromet, Dew, Parkinson, Cohen, & Schwartz, 1992; Estryn-Behar et al., 1990; Kawakami, Haratani, & Araki, 1992; S. Stansfeld & Candy, 2006; S. A. Stansfeld et al., 1999), as well as a higher risk for depression (Andrea, Bultmann, Van Amelsvoort, & Kant, 2009; Bultmann, Kant, Schroer, & Kasl, 2002; Niedhammer, Goldberg, Leclerc, Bugel, & David, 1998; S. Stansfeld & Candy, 2006). More recently, a longitudinal cohort study revealed that job demand had a stronger influence on the onset of depression than changes in job control (Smith & Bielecky, 2012). Other cohort studies have shown that women are more susceptible to major depression than men (Bebbington et al., 1998; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). Decreased left dorsolateral prefrontal cortex activity has consistently been found in depression (Drevets, 1999; Goodwin & Jamison, 2007). A previous NIRS study on healthy volunteers found a correlation between high apathy scores and decreased activation in the left prefrontal cortex during the VFT (Sawa et al., 2013). Most NIRS studies have also shown reduced brain activation during cognitive tasks in major depressive disorder (Noda et al., 2012; Schecklmann et al., 2011; Suto et al., 2004; Takizawa et al., 2014). The present findings, therefore, suggest that increased job demand may lead to the reduced left dorsolateral prefrontal cortex function we found among female participants. These results may imply the importance of stress-related prefrontal dysfunction as a mediating factor for female workers in developing mental illnesses, such as major depression.

The relationship between job control and frontotemporal cortex activity

We also found a positive correlation between job control and a level of activity in the right superior temporal region during the VFT, in both the total and male samples. Previous studies have reported that job control is associated with work absences due to mental health issues and depression (Hesketh & Shouksmith, 1986; Inoue et al., 2010). In line with our findings, a previous NIRS study found an association between reduced activation of the right superior temporal region during the VFT with a stronger subjective feeling of psychological fatigue (Suda et al., 2009). In contrast, however, an fMRI examination showed higher compensatory activation of the aforementioned region among participants after one night of sleep deprivation (Strangman, Thompson, Strauss, Marshburn, & Sutton, 2005). These varying results possibly indicate some differences between the effects of exposure to short-term and/or persistent stress on brain function. Further studies are required to elucidate the differential effect of length, quality, and quantity of stress on right superior temporal functions.

The relationship between job strain and frontotemporal cortex activity

The present study revealed an association between frontotemporal cortex activation and job stress according to gender; however, such an association was not applicable to the job strain index, which falls under the JDC model. In the JDC model, work characteristics fall into four categories, made up of a combination of job demand and job control. For example, a group that experiences high job demand with low job control is considered a "high strain" group. This group shows sensitivity in terms of its reaction to psychological stress. In addition, high strain has a negative effect on these individuals' health that can manifest as cardiovascular disease (Eller et al., 2009; Kivimaki et al., 2012), hypertension (Ohlin et al., 2007), and mental health problems, such as depressive symptoms and susceptibility to major depressive disorder (Bonde, 2008; Cropley et al., 1999; De Lange et al., 2003; Netterstrom et al., 2008; S. A. Stansfeld et al., 1999; Wang et al., 2009). Our findings suggest differential mechanisms of how job demand versus job control may influence the functional brain network. Future social epidemiology and neuroscience studies using the JDC model should be aware that using this simplified index of "job strain" might mask the real relationships between job-related stress and brain functional alterations.

Furthermore, the job demands-resources (JD-R) model (Demerouti, Bakker, Nachreiner, & Schaufeli, 2001), which contains both the JDC model and the effort-reward imbalance model, is recently proposed. The survey based on this model showed that the burnout mediates the relation between high job demands and health problems, while job resources including job control are associated with work engagement (Schaufeli & Bakker, 2004). The present results and the previous study presumably indicate that job demand serves a different function from job control.

The relationship between job stress and CES-D

Many follow-up studies showed that job-related stress is regarded as a moderately elevated risk of major depression. (Bonde, 2008; Netterstrom et al., 2008; Wang et al., 2009). In contrast, we found no significant correlation between job-related stress scores and CES-D scores. This discrepancy in the result may arise from the following methodological difference between the previous studies and our study. The previous studies recruited population-based participants including patients with psychiatric disease such as major depression disorder. In contrast, only healthy subjects participated in the present study by use of the exclusion criterion for any history of neurological or psychiatric disease (e.g., hemicrania, insomnia, major depression disorder, and pervasive developmental disorders), because of the elimination of the changes due to the neurological or psychiatric disease.

Additionally, we found a significant correlation between job-related stress scores and frontotemporal cortex activation. Our results suggest that high job stress induces frontotemporal cortex dysfunction in healthy subjects. Selye H proposed three response stages of chronic stress (alarm reaction, resistance, and exhaustion) in human (Selye, 1976). Physical or mental upset will appear to fight stress in stage of alarm reaction. If stress stimulus is exposed continuously, the stage of stress response moves to the stage of resistance. In this stage, it is noted that the body becomes accustomed to stress-induced changes, and the physiological indices such as autonomic function and one's subjective feeling improve temporarily. Our result is similar to the stage of resistance. The present finding showed that the brain function might be damaged by the chronic stress in the stage of resistance, in contrast to the peripheral physiological response and one's feeling. If the exposure of the stress persists chronically, the response stage is in transition to the stage of exhaustion developing a disease such as depression. At any rate, the present results implicate that job stress influences on the brain, regardless of the subjective depressive feelings.

Gender difference of frontotemporal cortex activity associated with job stress

Our results also showed gender differences in the association between JCQ and frontotemporal cortex activation. Many studies have previously suggested that the effects of job stress on health vary according to gender (Karasek, Gardell, & Lindell, 1987; Van Der Doef & Maes, 1999). The range of psychological distress relating to job stress is greater for men than women (Vermeulen & Mustard, 2000). Furthermore, female workers may be more sensitive to the impact of stress on health (Roxburgh, 1996). In other instances, psychological stress has been shown to affect brain function differently in men and women. In the current study, significant correlations between higher job control and greater [oxy-Hb] changes in the right temporal cortex were observed among men and in the total sample. Leueken et al. (2009) has reported that the central regulation of cortisol secretion is under excitatory control of the right hemisphere in patients with unilateral stroke and suggested that the region in the right hemisphere may affect response patterns of the hypothalamic–pituitary–adrenal axis. These results indicate that job control is related to brain function in the right hemisphere, and more broadly, the management of job control is vital for all workers' health.

Furthermore, job control is involved in the decision authority. Gender-related difference has been observed in the brain using a decision -making task; greater right hemisphere activation during a Iowa gambling task in men, whereas women demonstrated more left hemisphere activation (Bolla, Eldreth, Matochik, & Cadet, 2004). This is comparable to the present results of stronger correlation in men. Meanwhile, we found a significant correlation between higher job demand and smaller [oxy-Hb] changes in the left dorsolateral prefrontal cortex in women. Job demand represents quantitative workload such as working hard and pressure of work. In other words, it would appear that the extent of job demand assessed by self-reported questionnaire is related to negative emotional response of workload. The processing of emotional regulation including negative feeling varies by gender. Tranel and colleagues have reported that men with right-sided but not left-sided damage and women with left-sided but not right-sided damage show the altered social and emotional behaviors, following damage to limbic system including the medial prefrontal cortex (Tranel, Damasio, Denburg, & Bechara, 2005) or the amygdala (Tranel & Bechara, 2009). Dorsolateral prefrontal cortex plays a role in the emotional regulation along with limbic system (Davidson, 2002). Previous functional brain imaging studies have shown that female participants reduced activity in the dorsolateral prefrontal cortex while watching stressful movie (Qin et al., 2009). Another NIRS studies showed that prefrontal cortex activation during the exposure to negative stimuli (Yang et al., 2007) was differed by gender. Taken together, the association of high job demand and small activation in the left dorsolateral prefrontal cortex in women might be regarded as the dysfunction in emotional processing. These results suggest that stress response might depend on different brain structure and function for men and women.

LIMITATIONS

This study employed a cross-sectional design. Additionally, our model of the directional relationship between job-related stress and brain functioning may be too simple. There may be bidirectional relationships between a stressful environment and brain characteristics; namely, it is possible that a person's stress-coping ability and brain functioning can affect his/her social adjustment and job-related environment. Future longitudinal investigations should be conducted to assess the causal link between social stratification and job-related stress, as well as individual characteristics of personality and stress-coping styles, brain functioning, and consequent health problems (Wang et al., 2009).

CONCLUSION

This study integrated social, neuro, and public health sciences to identify possible individual and policy interventions to resolve an emerging worldwide issue of social stratification determinants of health.

Original manuscript received 27 July 2014
Revised manuscript accepted 5 December 2014
First published online 12 January 2015

REFERENCES

Andrea, H., Bultmann, U., Van Amelsvoort, L. G., & Kant, Y. (2009). The incidence of anxiety and depression among employees – the role of psychosocial work characteristics. *Depress Anxiety*, *26*, 1040–1048. doi:10.1002/da.20516

Arnsten, A. F. (2007). Catecholamine and second messenger influences on prefrontal cortical networks of "representational knowledge": A rational bridge between genetics and the symptoms of mental illness. *Cerebral Cortex*, *17* (Suppl 1), i6–15. doi:10.1093/cercor/bhm033

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*, 410–422. doi:10.1038/nrn2648

Bebbington, P. E., Dunn, G., Jenkins, R., Lewis, G., Brugha, T., Farrell, M., & Meltzer, H. (1998). The influence of age and sex on the prevalence of depressive conditions: Report from the National Survey of Psychiatric Morbidity. *Psychological Medicine*, *28*, 9–19. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9483679

Benach, J., Muntaner, C., Santana, V., & the Employment Conditions Knowledge Network (EMCONET). (2007). *Employment conditions and health inequalities*. Geneva: WHO.

Berkman, L., & Kawachi, I. (2000). A historical framework for social epidemiology. In B. Lf & I. Kawachi (Eds.), *Social epidemiology* (pp. 3–12). New York, NY: Oxford University Press.

Bolla, K. I., Eldreth, D. A., Matochik, J. A., & Cadet, J. L. (2004). Sex-related differences in a gambling task and its neurological correlates. *Cerebral Cortex*, *14*, 1226–1232. doi:10.1093/cercor/bhh083

Bonde, J. P. (2008). Psychosocial factors at work and risk of depression: A systematic review of the epidemiological evidence. *Occupational and Environmental Medicine*, *65*, 438–445. doi:10.1136/oem.2007.038430

Broadbent, D. E. (1985). The clinical impact of job design. *British Journal of Clinical Psychology*, *24*(1), 33–44. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3971067

Bromet, E. J., Dew, M. A., Parkinson, D. K., Cohen, S., & Schwartz, J. E. (1992). Effects of occupational stress on the physical and psychological health of women in a microelectronics plant. *Social Science & Medicine*, *34*, 1377–1383. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1529375

Bultmann, U., Kant, I. J., Schroer, C. A., & Kasl, S. V. (2002). The relationship between psychosocial work characteristics and fatigue and psychological distress. *International Archives of Occupational and Environmental Health*, *75*, 259–266. doi:10.1007/s00420-001-0294-0

Cahill, L. (2006). Why sex matters for neuroscience. *Nature Reviews Neuroscience*, *7*, 477–484. doi:10.1038/nrn1909

Cropley, M., Steptoe, A., & Joekes, K. (1999). Job strain and psychiatric morbidity. *Psychological Medicine*, *29*, 1411–1416. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10616947

Davidson, R. J. (2002). Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biological Psychiatry*, *51*, 68–80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11801232

De Lange, A. H., Taris, T. W., Kompier, M. A., Houtman, I. L., & Bongers, P. M. (2003). "The very best of the millennium": Longitudinal research and the demand-control-(support) model. *Journal of Occupational Health Psychology*, *8*, 282–305. doi:10.1037/1076-8998.8.4.282

De Smet, P., Sans, S., Dramaix, M., Boulenguez, C., De Backer, G., Ferrario, M., & Kornitzer, M. (2005). Gender and regional differences in perceived job stress across Europe. *The European Journal of Public Health*, *15*, 536–545. doi:10.1093/eurpub/cki028

Delpy, D. T., Cope, M., Van Der Zee, P., Arridge, S., Wray, S., & Wyatt, J. (1988). Estimation of optical path length through tissue from direct time of flight measurement. *Physics in Medicine and Biology*, *33*, 1433–1442. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3237772

Demerouti, E., Bakker, A. B., Nachreiner, F., & Schaufeli, W. B. (2001). The job demands-resources model of burnout. *Journal of Applied Psychology*, *86*, 499–512. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11419809

Drevets, W. C. (1999). Prefrontal cortical-amygdalar metabolism in major depression. *Annals of the New York Academy of Sciences*, *877*, 614–637. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10415674

Drevets, W. C. (2000). Neuroimaging studies of mood disorders. *Biological Psychiatry*, *48*, 813–829. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11063977

Eller, N. H., Netterstrom, B., Gyntelberg, F., Kristensen, T. S., Nielsen, F., Steptoe, A., & Theorell, T. (2009). Work-related psychosocial factors and the development of ischemic heart disease: A systematic review. *Cardiology in Review*, *17*, 83–97. doi:10.1097/CRD.0b013e318198c8e9

Estryn-Behar, M., Kaminski, M., Peigne, E., Bonnet, N., Vaichere, E., Gozlan, C., & Giorgi, M. (1990). Stress at work and mental health status among female hospital workers. *British Journal of Industrial Medicine*, *47*, 20–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2310704

Goodwin, F. K., & Jamison, K. R. (2007). *Manic-depressive illness: Bipolar disorders and recurrent depression* (2nd ed.). New York, NY: Oxford University Press.

Hesketh, B., & Shouksmith, G. (1986). Job and non-job activities, job satisfaction and mental health among veterinarians. *Journal of Organizational Behavior*, *7*, 325–339. doi:10.1002/job.4030070406

Hoddes, E., Dement, W. C., & Zarcone, V. (1971). The history and use of the Stanford sleepiness scale. *Psychophysiology*, *9*, 150.

Holmes, A., & Wellman, C. L. (2009). Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neuroscience & Biobehavioral Reviews*, *33*, 773–783. doi:10.1016/j.neubiorev.2008.11.005

Inoue, A., Kawakami, N., Haratani, T., Kobayashi, F., Ishizaki, M., Hayashi, T., & Araki, S. (2010). Job stressors and long-term sick leave due to depressive disorders among Japanese male employees: Findings from the Japan Work Stress and Health Cohort study. *Journal of Epidemiology & Community Health*, *64*, 229–235. doi:10.1136/jech.2008.085548

Kameyama, M., Fukuda, M., Yamagishi, Y., Sato, T., Uehara, T., Ito, M., & Mikuni, M. (2006). Frontal lobe function in bipolar disorder: A multichannel near-infrared spectroscopy study. *Neuroimage*, *29*, 172–184. doi:10.1016/j.neuroimage.2005.07.025

Karasek, R., Baker, D., Marxer, F., Ahlbom, A., & Theorell, T. (1981). Job decision latitude, job demands, and cardiovascular disease: A prospective study of Swedish men. *American Journal of Public Health*, *71*, 694–705. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7246835

Karasek, R., Gardell, B., & Lindell, J. (1987). Work and non-work correlates of illness and behaviour in male and female Swedish white collar workers. *Journal of Organizational Behavior*, *8*, 187–207. doi:10.1002/job.4030080302

Karesek, R., & Theorell, T. (1990). *Healthy work. stress, productivity and the reconstruction of work life*. New York, NY: Basic Books.

Kawakami, N., & Fujigaki, Y. (1996). Reliability and validity of the Japanese version of Job Content Questionnaire: Replication and extension in computer company employees. *Industrial Health*, *34*, 295–306. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8908841

Kawakami, N., Haratani, T., & Araki, S. (1992). Effects of perceived job stress on depressive symptoms in blue-collar workers of an electrical factory in Japan. *Scandinavian Journal of Work, Environment & Health*, *18*, 195–200. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1615294

Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *Journal of Affective Disorders*, *29*, 85–96. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8300981

Kivimaki, M., Nyberg, S. T., Batty, G. D., Fransson, E. I., Heikkila, K., Alfredsson, L., & Theorell, T. (2012). Job strain as a risk factor for coronary heart disease: A collaborative meta-analysis of individual participant data. *Lancet*, *380*, 1491–1497. doi:10.1016/S0140-6736(12)60994-5

Li, J., Yang, W., & Cho, S.-I. (2006). Gender differences in job strain, effort-reward imbalance, and health functioning among Chinese physicians. *Social Science & Medicine*, *62*, 1066–1077. doi:10.1016/j.socscimed.2005.07.011

Liston, C., McEwen, B. S., & Casey, B. J. (2009). Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proceedings of the National Academy of Sciences*, *106*, 912–917. doi:10.1073/pnas.0807041106

Lueken, U., Leisse, M., Mattes, K., Naumann, D., Wittling, W., & Schweiger, E. (2009). Altered tonic and phasic cortisol secretion following unilateral stroke. *Psychoneuroendocrinology*, *34*, 402–412. doi:10.1016/j.psyneuen.2008.10.002

Matsuoka, K., Uno, M., Kasai, K., Koyama, K., & Kim, Y. (2006). Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. *Psychiatry and Clinical Neuroscience*, *60*, 332–339. doi:10.1111/j.1440-1819.2006.01510.x

McEwen, B. S., & Morrison, J. H. (2013). The Brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron*, *79*, 16–29. doi:10.1016/j.neuron.2013.06.028

Netterstrom, B., Conrad, N., Bech, P., Fink, P., Olsen, O., Rugulies, R., & Stansfeld, S. (2008). The relation between work-related psychosocial factors and the development of depression. *Epidemiologic Reviews*, *30*, 118–132. doi:10.1093/epirev/mxn004

Niedhammer, I., Goldberg, M., Leclerc, A., Bugel, I., & David, S. (1998). Psychosocial factors at work and subsequent depressive symptoms in the Gazel cohort. *Scandinavian Journal of Work, Environment & Health*, *24*, 197–205. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9710372

Noda, T., Yoshida, S., Matsuda, T., Okamoto, N., Sakamoto, K., Koseki, S., & Higuchi, T. (2012). Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: A multi-channel near-infrared spectroscopy study. *Journal of Psychiatric Research*, *46*, 905–912. doi:10.1016/j.jpsychires.2012.04.001

Ohira, H., Matsunaga, M., Kimura, K., Murakami, H., Osumi, T., Isowa, T., & Yamada, J. (2011). Chronic stress modulates neural and cardiovascular responses during reversal learning. *Neuroscience*, *193*, 193–204. doi:10.1016/j.neuroscience.2011.07.014

Ohlin, B., Berglund, G., Rosvall, M., & Nilsson, P. M. (2007). Job strain in men, but not in women, predicts a significant rise in blood pressure after 6.5 years of follow-up. *Journal of Hypertension*, *25*, 525–531. doi:10.1097/HJH.0b013e32801220fa

Okamoto, M., Dan, H., Sakamoto, K., Takeo, K., Shimizu, K., Kohno, S., & Dan, I. (2004). Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping. *Neuroimage*, *21*, 99–111. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14741647

Qin, S., Hermans, E. J., Van Marle, H. J., Luo, J., & Fernandez, G. (2009). Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex. *Biological Psychiatry*, *66*, 25–32. doi:10.1016/j.biopsych.2009.03.006

Roxburgh, S. (1996). Gender differences in work and well-being: Effects of exposure and vulnerability. *Journal of Health and Social Behavior*, *37*, 265–277. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8898497

Sawa, M., Yamashita, H., Fujimaki, K., Okada, G., Takahashi, T., & Yamawaki, S. (2013). Negative correlation between affective symptoms and prefrontal activation during a verbal fluency task: A near-infrared spectroscopy study. *Neuropsychobiology*, *67*, 103–110. doi:10.1159/000345161

Schaufeli, W. B., & Bakker, A. B. (2004). Job demands, job resources, and their relationship with burnout and engagement: A multi-sample study. *Journal of Organizational Behavior*, *25*, 293–315. doi:10.1002/job.248

Schecklmann, M., Dresler, T., Beck, S., Jay, J. T., Febres, R., Haeusler, J., & Fallgatter, A. J. (2011). Reduced prefrontal oxygenation during object and spatial visual working memory in unpolar and bipolar depression. *Psychiatry Research: Neuroimaging*, *194*, 378–384. doi:10.1016/j.pscychresns.2011.01.016

Selye, H. (1976). Forty years of stress research: Principal remaining problems and misconceptions. *Canadian Medical Association Journal*, *115*, 53–56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1277062

Shima, S., Shikano, T., Kitamura, T., & Asai, M. (1985). New self-rating scale for depression. *Seishin Igaku (Clinical Psychiatry)*, *27*, 717–723. (in Japanese).

Singh, A. K., & Dan, I. (2006). Exploring the false discovery rate in multichannel NIRS. *Neuroimage*, *33*, 542–549. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16959498

Smith, P. M., & Bielecky, A. (2012). The impact of changes in job strain and its components on the risk of depression. *American Journal of Public Health*, *102*, 352–358. doi:10.2105/AJPH.2011.300376

Stansfeld, S., & Candy, B. (2006). Psychosocial work environment and mental health – a meta-analytic review. *Scandinavian Journal of Work, Environment & Health*, *32*, 443–462. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17173201

Stansfeld, S. A., Fuhrer, R., Shipley, M. J., & Marmot, M. G. (1999). Work characteristics predict psychiatric disorder: Prospective results from the Whitehall II Study. *Occupational and Environmental Medicine*, *56*, 302–307. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10472303

Strangman, G., Thompson, J. H., Strauss, M. M., Marshburn, T. H., & Sutton, J. P. (2005). Functional brain imaging of a complex navigation task following one night of total sleep deprivation: A preliminary study. *Journal of Sleep Research*, *14*, 369–375. doi:10.1111/j.1365-2869.2005.00488.x

Suda, M., Fukuda, M., Sato, T., Iwata, S., Song, M., Kameyama, M., & Mikuni, M. (2009). Subjective feeling of psychological fatigue is related to decreased reactivity in ventrolateral prefrontal cortex. *Brain Research*, *1252*, 152–160. doi:10.1016/j.brainres.2008.11.077

Suto, T., Fukuda, M., Ito, M., Uehara, T., & Mikuni, M. (2004). Multichannel near-infrared spectroscopy in depression and schizophrenia: Cognitive brain activation study. *Biological Psychiatry*, *55*, 501–511. doi:10.1016/j.biopsych.2003.09.008

Takada, M., Kondo, N., & Hashimoto, H. (2014). Japanese study on stratification, health, income, and neighborhood: Study protocol and profiles of participants. *Journal of Epidemiology*, *24*, 334–344. doi:10.2188/jea.JE20130084

Takizawa, R., Fukuda, M., Kawasaki, S., Kasai, K., Mimura, M., Pu, S., & Okazaki, Y. (2014). Neuroimaging-aided differential diagnosis of the depressive state. *Neuroimage*, *85*(Pt 1), 498–507. doi:10.1016/j.neuroimage.2013.05.126

Takizawa, R., Nishimura, Y., Yamasue, H., & Kasai, K. (2013). Anxiety and performance: The disparate roles of prefrontal subregions under maintained psychological stress. *Cerebral Cortex*, *24*, 1858–1866. doi:10.1093/cercor/bht036

Toronov, V., Webb, A., Choi, J. H., Wolf, M., Michalos, A., Gratton, E., & Hueber, D. (2001). Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. *Medical Physics*, *28*, 521–527. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11339749

Tranel, D., & Bechara, A. (2009). Sex-related functional asymmetry of the amygdala: Preliminary evidence using a case-matched lesion approach. *Neurocase*, *15*, 217–234. doi:10.1080/13554790902775492

Tranel, D., Damasio, H., Denburg, N. L., & Bechara, A. (2005). Does gender play a role in functional asymmetry of ventromedial prefrontal cortex? *Brain*, *128*, 2872–2881. doi:10.1093/brain/awh643

Tsuzuki, D., Jurcak, V., Singh, A. K., Okamoto, M., Watanabe, E., & Dan, I. (2007). Virtual spatial registration of stand-alone fNIRS data to MNI space. *Neuroimage*, *34*, 1506–1518. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17207638

Van Der Doef, M., & Maes, S. (1999). The job demand-control (-support) model and psychological well-being: A review of 20 years of empirical research. *Work & Stress*, *13*, 87–114. doi:10.1080/026783799296084

Vanagas, G., Bihari-Axelsson, S., & Vanagiene, V. (2004). Do age, gender and marital status influence job strain development for general practitioner? *Medicina (Kaunas)*, *40*, 1014–1018. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15516827

Vermeulen, M., & Mustard, C. (2000). Gender differences in job strain, social support at work, and psychological distress. *Journal of Occupational Health Psychology*, *5*, 428–440. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11051526

Wang, J., Korczykowski, M., Rao, H., Fan, Y., Pluta, J., Gur, R. C., & Detre, J. A. (2007). Gender difference in neural response to psychological stress. *Social Cognitive and Affective Neuroscience*, *2*, 227–239. doi:10.1093/scan/nsm018

Wang, J., Schmitz, N., Dewa, C., & Stansfeld, S. (2009). Changes in perceived job strain and the risk of major depression: Results from a population-based longitudinal study. *American Journal of Epidemiology*, *169*, 1085–1091. doi:10.1093/aje/kwp037

Yang, H., Zhou, Z., Gong, H., Luo, Q., & Lu, Z. (2009). Sex differences in prefrontal hemodynamic response to mental arithmetic as assessed by near-infrared spectroscopy. *Gender Medicine*, *6*, 565–574. doi:10.1016/j.genm.2009.11.003

Yang, H., Zhou, Z., Liu, Y., Ruan, Z., Gong, H., Luo, Q., & Lu, Z. (2007). Gender difference in hemodynamic responses of prefrontal area to emotional stress by near-infrared spectroscopy. *Behavioural Brain Research*, *178*, 172–176. doi:10.1016/j.bbr.2006.11.039

CORTEX 58 (2014) 23–26

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Letter to the editor

Genetic risk variants of schizophrenia associated with left superior temporal gyrus volume

Kazutaka Ohi [a,b], *Ryota Hashimoto* [a,c,*], *Masashi Ikeda* [d], *Fumio Yamashita* [e], *Masaki Fukunaga* [f], *Kiyotaka Nemoto* [g], *Takashi Ohnishi* [h,i], *Hidenaga Yamamori* [a,j], *Yuka Yasuda* [a], *Michiko Fujimoto* [a], *Satomi Umeda-Yano* [j], *Yoshiyuki Watanabe* [k], *Nakao Iwata* [d], *Daniel R. Weinberger* [l] and *Masatoshi Takeda* [a,c]

[a] *Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan*
[b] *National Hospital Organization, Yamato Mental-Medical Center, Nara, Japan*
[c] *Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Osaka, Japan*
[d] *Department of Psychiatry, Fujita Health University School of Medicine, Aichi, Japan*
[e] *Division of Ultrahigh Field MRI, Institute for Biomedical Sciences, Iwate Medical University, Iwate, Japan*
[f] *Biofunctional Imaging, Immunology Frontier Research Center, Osaka University, Osaka, Japan*
[g] *Department of Neuropsychiatry, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan*
[h] *Department of Psychosomatic Research, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan*
[i] *CNS Science Department, Scientific Affairs Division, Janssen Pharmaceutical K.K., Tokyo, Japan*
[j] *Department of Molecular Neuropsychiatry, Osaka University Graduate School of Medicine, Osaka, Japan*
[k] *Department of Radiology, Osaka University Graduate School of Medicine, Osaka, Japan*
[l] *Lieber Institute for Brain Development, Johns Hopkins University Medical Campus, Baltimore, MD, USA*

ARTICLE INFO

Article history:
Received 11 January 2014
Revised 4 April 2014
Accepted 21 May 2014
Published online 4 June 2014

Schizophrenia is a common and complex psychiatric disease with a high estimated heritability of approximately 80% (Sullivan, Kendler, & Neale, 2003), and hundreds of common single-nucleotide polymorphisms (SNPs) are weakly implicated in the pathogenesis of schizophrenia (Purcell et al., 2009). Gray matter volume (GM) in brain also has an estimated heritability of approximately 60–90% in healthy subjects (Thompson et al., 2001) and reduced GM volumes in patients with schizophrenia have been frequently reported (Chan, Di, McAlonan, & Gong, 2011). A single polygenic

* *Corresponding author*. Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, D3, 2-2, Yamadaoka, Suita, Osaka, 565-0871, Japan.
E-mail address: hashimor@psy.med.osaka-u.ac.jp (R. Hashimoto).
http://dx.doi.org/10.1016/j.cortex.2014.05.011