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168 *Current Molecular Medicine* 2015, *15,* 168-175

Imaging Genetics and Psychiatric Disorders

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Abstract: Imaging genetics is an integrated research method that uses neuroimaging and genetics to assess the impact of genetic variation on brain function and structure. Imaging genetics is both a tool for the discovery of risk genes for psychiatric disorders and a strategy for characterizing the neural systems affected by risk gene variants to elucidate quantitative and mechanistic aspects of brain function implicated in psychiatric disease. Early studies of imaging genetics included association analyses between brain morphology and single nucleotide polymorphisms whose function is well known, such as catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF). GWAS of psychiatric disorders have identified genes with unknown functions, such as ZNF804A, and imaging genetics has been used to investigate clues of the biological function of these genes. The difficulty in replicating the findings of studies with small sample sizes has motivated the creation of large-scale collaborative consortiums, such as ENIGMA, CHARGE and IMAGEN, to collect thousands of images. In a genome-wide association study, the ENIGMA consortium successfully identified common variants in the genome associated with hippocampal volume at 12q24, and the CHARGE consortium replicated this finding. The new era of imaging genetics has just begun, and the next challenge we face is the discovery of small effect size signals from large data sets obtained from genetics and neuroimaging. New methods and technologies for data reduction with appropriate statistical thresholds, such as polygenic analysis and parallel independent component analysis (ICA), are warranted. Future advances in imaging genetics will aid in the discovery of genes and provide mechanistic insight into psychiatric disorders.


R. Hashimoto

Keywords: Bipolar disorder, genome-wide association study, gene, imaging genetics, intermediate phenotype, neuroimaging, schizophrenia, structural MRI.

IMAGING GENETICS AND PSYCHIATRIC DISORDERS

Imaging genetics is an integrated research method that uses neuroimaging and genetics to assess the impact of genetic variations on brain function and structure. In psychiatric genetics, brain function and structure are so-called “intermediate phenotypes” that could be postulated to lie closer to the biological pathway of genes than the psychiatric disorder itself [1] (Fig. **1**). Intermediate phenotypes should be heritable, exhibit good psychometric properties, be related to the disorder and its symptoms in the general population, be stable over time, show increased expression in the unaffected relatives of probands, cosegregate with the disorder in families, and have common genetic influences on the disorder [1]. Intermediate phenotypes might be a more direct index of the physiological effects of genetic variations of risk genes than the diagnosis of psychiatric disorders. There are two concepts of imaging genetics as an intermediate phenotype (Fig. **2**). One concept is that imaging genetics is a tool for the discovery of risk genes for psychiatric disorders; the other concept is that imaging genetics is a strategy for characterizing the neural systems affected by risk gene variants to elucidate the

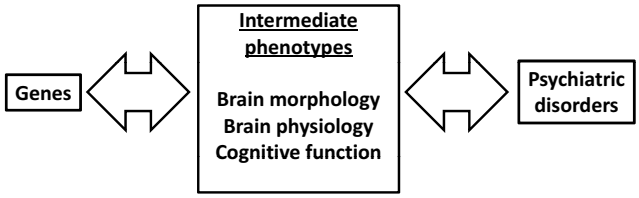

Fig. (1). Genes, intermediate phenotypes and psychiatric disorders.

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quantitative and mechanistic aspects of brain function implicated in psychiatric disease. These two concepts have different hypotheses, but the methods to test the hypotheses are the same and include association analyses between neuroimaging data and genetic variations.

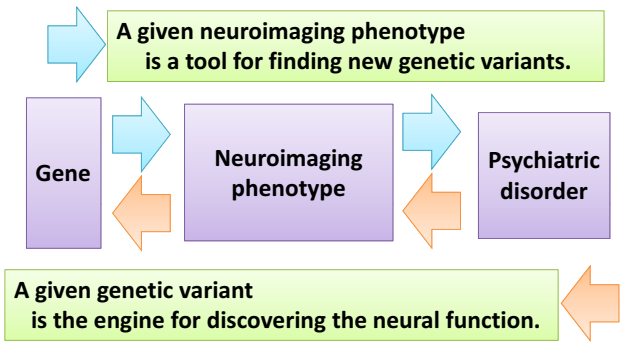

Fig. (2). Two concepts of imaging genetics.

Several excellent reviews of functional neuroimaging as intermediate phenotypes exist. However, few reviews focus on structural neuroimaging as an intermediate phenotype [1-3]. Therefore, in this review, we have updated the imaging genetics of structural magnetic resonance imaging (MRI) of gray matter and brain regional volume.

CANDIDATE GENE ANALYSIS

Early studies of imaging genetics included association analyses between brain morphology and a single nucleotide polymorphism whose function was well known. Numerous researchers tested their hypotheses using imaging genetics according to the function of the Val158Met single nucleotide polymorphism (SNP) of catechol-O-methyltransferase (COMT), the Val66Met SNP of brain-derived neurotrophic factor (BDNF), and the Ser704Cys SNP of disrupted-in-schizophrenia 1 (DISC1), among other genes.

The COMT gene is one of the most frequently investigated gene targets of functional imaging genetics and structural imaging genetics [3, 4]. COMT is a major mammalian enzyme involved in the metabolic degradation of catecholamines; this activity is higher in the Val158 protein than in the Met158 protein. The Val158 genotype was associated with lower executive performance, less efficient physiological response in the prefrontal cortex and a risk for schizophrenia [5]. Many subsequent neuroimaging studies using structural MRI have been reported using the functional imaging genetics method. Four of six studies in healthy controls or the general population in adults and children showed decreased hippocampal gray matter volume in the Val158 allele [6-9], although two studies failed to replicate this finding [10, 11]. Two studies in patoemts schizophrenia and individuals at high genetic risk for schizophrenia had smaller gray matter density in the anterior cingulate cortex [12, 13]. Five studies demonstrated genotype effects of the COMT Val158Met allele on the dorsolateral prefrontal cortex (DLPFC) or the frontal lobe volume in healthy subjects and in patients with velo-cardio-facial-syndrome, but the directions of the effects of the Val158 allele were inconsistent [6, 7, 10, 14, 15].

BDNF modulates hippocampal plasticity and hippocampal-dependent memory in cell models and animals. BDNF is a very important molecule in the neuroscience field, and it has also been implicated in several neuropsychiatric disorders [16]. The functional Val66Met polymorphism is well studied in imaging genetics. At the cellular level, the Met66-type BDNF protein showed a lower depolarization-induced secretion of BDNF and failed to localize to secretory granules or synapses compared to the Val66-type BDNF protein [17]. That study also indicated that Met66 was associated with poorer episodic memory, abnormal hippocampal activation and lower hippocampal n-acetyl aspartate (NAA) in human subjects. There are more than 20 association studies between the BDNF Val66Met SNP and hippocampal volume. A recent systematic review and meta-analysis analyzed 25 studies including healthy controls and patients with schizophrenia, bipolar disorder, and major depressive disorder and showed that carrying a met allele at the BDNF val66met locus is associated with lower hippocampal volumes [18]. However, this effect was very small (Cohen's d = 0.13), and there was a publication bias. This review questioned whether the observed effect was a genuine biological effect of the met allele or subject to a winner's curse, with large effect sizes found in a few early studies and increasingly smaller effect sizes in later studies. Four studies examined the gene-environment interaction between BDNF Val66Met and childhood abuse in healthy controls and in patients with psychiatric disease. Three studies showed reduced hippocampal volume in Met carriers with childhood abuse or early life stress [19-21], and one study demonstrated a smaller volume of the anterior cingulate cortex in Met carriers with a history of childhood adversity [22]. Few studies reported an association between gray matter volume reduction related to disease progression and BDNF Val66Met, which would be suspected because BDNF is an essential neurotrophic factor in the brain. Met allele carriers had significantly greater reductions in frontal gray matter volume over an average of 3 years with schizophrenia [23]. Consistent with this reported reduction, Met allele carriers with schizophrenia had an age-associated volume reduction [24], and progressive atrophy in the frontal cortex in Alzheimer's disease patients who converted from mild cognitive impairment was greater in Met carriers [25].

Chromosome translocation analysis first identified DISC1 as a candidate gene for psychiatric illness, and this gene segregated with schizophrenia, bipolar disorder and major depressive disorder in a single pedigree [26]. A substantial body of evidence demonstrated the role of this gene in multiple pathways, such as cell migration, neurite organization, the cytoskeleton, mitochondrial function and glutamate

signaling, implicated in psychiatric disorders [27]. The Ser704Cys SNP in the DISC1 gene has been studied extensively in imaging genetics because this SNP is a functional SNP. The Cys704-type DISC1 protein showed less ERK activation compared to the Ser704-type DISC1 protein in primary neuron cultures [28]. ERK is a key molecule in neuronal plasticity, development and death. A recent systematic review summarized the effects of the Ser704Cys SNP on volumes in frontal and hippocampal regions [29]. The results of four studies in frontal regions have not been replicated, and four reports focusing on hippocampal structures were inconsistent. Six studies examined the volumetric effects of the Leu607Phe SNP, but their results have not been replicated.

Association studies between other genes that are implicated in psychiatric disorders, especially schizophrenia, such as dystrobrevin binding protein 1 (DTNBP1), neuregulin-1 (NRG1), and v-akt murine thymoma viral oncogene homolog 1 (AKT1), and brain regional volumes have been reported. Four studies examined the association between a SNP or schizophrenia-risk haplotype in DTNBP1 and hippocampal, prefrontal, and total brain volumes. Three studies found an influence of genetic variants on brain volumes in different regions, but one study failed to find this association [30-33]. Two NRG1 studies showed an association of a SNP or schizophrenia-risk haplotype and temporal region volumes [34, 35], but another study failed to replicate those findings [31]. Two studies concerning the AKT1 gene reported an association with gray matter volumes in the frontostriatal and parietal areas [36, 37]. Although several positive results in DTNBP1, NRG1 and AKT1 have been reported, the results remain difficult to interpret because of the unknown function of associated SNPs or haplotypes.

RISK GENE ANALYSIS IDENTIFIED BY GWAS

Imaging genetics can promote an understanding of the genetic basis of psychiatric disorders. This method also contributes fundamental insights into basic neuroscience. Genome-wide association studies (GWAS) of psychiatric disorders, such as schizophrenia, bipolar disorder, and major depressive disorder, have been reported in this decade [38]. The first reports of GWAS demonstrated several loci associated with psychiatric disorders, such as ZNF804A, neurogranin (NRGN), and the major histocompatibility complex (MHC) region, at a widely used benchmark for genome-wide significance ($p<5.0\times10^{-8}$) in 2008 and 2009. The biological functions of many of these genes are unknown. Therefore, imaging genetics have been used as a tool to investigate the biological function of these genes.

The SNP rs1344706 in the ZNF804A gene was associated with schizophrenia in the first GWAS [39]; the biological function of this gene was unknown at the time. Three structural imaging genetics studies were reported. Lencz *et al*. reported that risk allele homozygotes showed reduced gray matter volumes in several regions, including the angular gyrus, parahippocampal gyrus, posterior cingulate, and medial orbitofrontal gyrus/gyrus rectus, in healthy subjects when controlling for white matter volumes [40]. The authors also showed larger white matter volume in risk allele homozygotes. The second study demonstrated that risk allele carriers showed relatively larger gray matter volumes than that in non-risk allele carriers, particularly hippocampal volumes, in patients with schizophrenia [41]. The final study showed no significant impact of rs1344706 on gray matter volume, but this SNP influenced white matter volume in patients with schizophrenia and controls in opposite directions [42]. The rs12807809 SNP in NRGN is a genetic risk variant with genome-wide significance for schizophrenia [43]. NRGN plays an important role in the Ca^{2+}–CaM signaling pathway, including the postsynaptic activation of CaM-dependent protein kinase II (CaMKII) by CaM, which is associated with strengthened N-methyl-D-aspartate (NMDA) receptor signaling [44]. Ohi *et al*. first reported the association of rs12807809 with the gray matter volume of the anterior cingulate cortex in patients with schizophrenia and no effect of genotype on gray matter volume in healthy controls [45]. Two other studies showed an association between this SNP and cortical thickness, but in opposite directions [46, 47]. One marker in the MHC region, rs6904071, was associated with hippocampal volume and episodic memory [48].

A second stage of GWAS in schizophrenia was reported using the first stage GWAS to increase the sample size. This second stage found more risk genes, such as the Cyclin M2 (CNNM2), micro RNA 137 (MIR137), PCGEM1, tripartite motif-containing protein 26 (TRIM26), CUB and Sushi multiple domains 1 (CSMD1), matrix metallopeptidase 16 (MMP16), 5'-nucleotidase, cytosolic II (NT5C2) and coiled-coil domain containing 68 (CCDC68) genes [49]. The risk variant rs7914558 in the CNMM2 gene was associated with the volume of the bilateral inferior frontal gyri, and no significant association between other risk genes and gray matter morphology was observed [50]. However, another research group showed an increased gray matter volume in the temporal pole and the anterior cingulate cortex in subjects with a risk allele in the CNNM2 [51]. The same group also reported no association of the risk SNP in CSMD1 and gray matter volume [52]. Collaborative genome-wide association analysis supports a role for calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C) and ankyrin 3 (ANK3) in bipolar disorder [53]. Healthy subjects with risk allele carriers showed significantly increased gray matter volume in a corticolimbic frontotemporal neural system compared to those without a risk allele [54]. A risk allele of ANK3 was associated with cortical thinning in patients with first-episode psychosis [55]. However, Tesli *et al*. reported no association between the brain structural measures found in bipolar disorder, including gray matter volumes, and nine SNPs in the genes CACNA1C, ANK3, odd Oz/ten-m homolog 4 (ODZ4) and spectrin repeat containing nuclear envelope 1 (SYNE1) [56].

Overall, the effects of the risk SNPs in the risk genes identified by recent GWASs on brain structure have not been consistent. This inconsistency may be due to the very small number of studies reported for each gene/SNP, the small sample sizes, and differences in the methodology of brain morphological measurements and in the tested anatomical regions. Therefore, further replication studies using larger sample sizes are necessary to draw conclusions.

GENOME-WIDE ASSOCIATION OF NEUROIMAGING STUDY

Recently, several genome-wide association studies using neuroimaging as a phenotype have been reported. These studies sought new genetic variations to explain the risk for neuropsychiatric disorders and the underlying mechanisms of brain structure and function. A larger sample size compared to that of a candidate gene approach can be assumed because the significant p value threshold is very strict (<5.0 x 10-8) in GWAS.

In the early stage of GWAS brain morphology, the Alzheimer's Disease Neuroimaging Initiative (ADNI) performed a genome-wide association study using over 400,000 SNPs and brain structures in less than 1000 subjects, including healthy controls, individuals with mild cognitive impairment and Alzheimer's disease patients. This research group used several brain phenotypes, including temporal lobe volume; more than 30,000 voxels calculated using tensor-based morphometry; and 142 measures of gray matter density, volume, and cortical thickness by voxel-based morphometry (VBM) and FreeSurfer parcellation [57-59]. Although extensive efforts using structural phenotypes and different strategies have been made, these studies have failed to identify new genetic variants with genome-wide significance. This failure may be due to the small effect size of each true genetic variant, and researchers in the imaging genetics field have enthusiastically formed a large consortium to increase sample sizes and detect signals.

Several large-scale collaborative consortiums have been established to overcome the problem of sample size, including the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium [60], the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium [61], and the IMAGEN study [62]. The ENIGMA Consortium is a collaborative network of researchers working together on a range of large-scale studies that integrate data from 70 institutions worldwide. ENIGMA studies have analyzed neuroimaging data from more than 12,826 subjects. ENIGMA's first project was a genome-wide association study identifying common genomic variants associated with hippocampal or intracranial volume [63]. The intergenic variant rs7294919, located at 12q24.22, was associated with hippocampal volume, and rs10784502, located within HMGA2 at 12q14.3, was associated with intracranial volume. Researchers continue to explore genetic associations with subcortical volumes (ENIGMA2) and white matter microstructure (ENIGMA-DTI). Working groups are also focused on understanding the impact of schizophrenia, bipolar illness, major depression and attention deficit/hyperactivity disorder (ADHD) on the brain.

The CHARGE Consortium was formed to facilitate genome-wide association study meta-analyses and replication opportunities among multiple large and well-phenotyped longitudinal cohort studies. The primary focus of the CHARGE Consortium is heart and aging research, but GWAS of brain morphology are parts of their GWAS. CHARGE replicated the ENIGMA GWAS results, which included the association of common variants at 12q14 and 12q24 with hippocampal volume using more than 10,000 population-based subjects [64]. IMAGEN is a European research project investigating mental health and risk-taking behavior in teenagers. These researchers are investigating the impact that certain attitudes, thinking styles, brain activity patterns and genetic characteristics have on teenage risk-taking behavior and mental health. Imaging genetics of structural MRI is one aspect of their projects, and the GWAS of structural neuroimaging are ongoing but have not been reported [65]. However, IMAGEN samples were used in the ENIGMA report, which identified a SNP associated with hippocampal volume. Hass *et al*. performed GWAS of hippocampal volume using 328 subjects, including healthy controls and schizophrenic patients, but no SNP reached genome-wide significance; thus, this study failed to replicate the ENIGMA and CHARGE findings [66]. This failure might have been due to the small sample size. Recently, our group performed GWAS of gray matter volume of superior frontal gyrus (SFG) in 378 controls and 158 patients with schizophrenia and found associations between five variants on 1p36.12 and the right SFG volume at a widely used benchmark for genome-wide significance [67]. The use of GWAS of structural neuroimaging has just begun, but this method appears very promising.

POLYGENIC RISK SCORE ANALYSIS

Polygenic risk score analysis has been developed recently to summarize the genetic components of schizophrenia risk and involves thousands of common alleles with very small effects [68]. A polygenic risk score for a particular disease can be calculated for each individual in a sample from published genetic association data by summing the known effect size of each individual SNP multiplied by the number of reference alleles present for that SNP in a particular individual. This method has shown that the polygenic risk component in schizophrenia also contributes to the risk of bipolar disorder but not to that of several non-psychiatric diseases [68]. This association is also true for a potential intermediate phenotype, general cognitive ability [69]. Using Cognitive Genomics consorTium (COGENT) samples, patients with schizophrenia had lower cognitive polygenic scores compared to controls, and the polygenic risk scores for patients with schizophrenia were associated with lower

general cognitive ability, thus indicating a genetic overlap between schizophrenia and general cognitive ability.

Recently, an association analysis between the schizophrenia polygenic risk score and brain volume has been reported [70, 71]. The polygenic risk score, which was calculated using the Psychiatric Genetics Consortium case control data, was associated with total brain volume and white matter volume, but not gray matter volume. Polygenic risk score for schizophrenia was associated with left superior temporal gyrus volume [71]. These early reports are association studies of the polygenic score and brain structure, and further replication studies, including studies of regional brain volume, are warranted in the near future.

LIMITATION OF IMAGING GENETICS

Twin studies have revealed that many aspects of brain structure, including gray matter volume, are highly heritable [72]. Brain measures also yield superior reproducibility for clinical diagnosis and cognitive examination [72]. The heritability and reproducibility of this brain measure are high, but this analysis has limitations. Brain volume may be altered by the environmental foactors, such as medication. Treatment with lithium for 4 weeks in patients with bipolar disorder increased brain gray matter volume [73]. Haloperidol treatment for two years in patients with first-episode schizophrenia resulted in significant decreases in gray matter volume, whereas olanzapine-treated patients did not show such decreases [74]. Even a single dose of baclofen administered two hours before an MRI scan decreased the gray matter signal in the dorsal rostral anterior cingulate, as calculated by VBM analysis [75]. Therefore, caution is required, particularly in patients using medications.

FUTURE DIRECTIONS

This review summarized the past and present status of imaging genetics (Fig. **3**). The technological development of genetic and neuroimaging approaches has introduced a new era of imaging genetics. GWAS using microarray DNA chips and rare variant analyses using next generation sequencing are two representative revolutions in genetics association studies. Both approaches can produce millions of genotype data points. Genetic association analysis of large amounts of data faces a critical issue in corrections for multiple testing. For example, the statistical significance of GWAS is generally set at $p < 5 \times 10^{-8}$. When the effect size of a genetic variant is small, such as the risk for a psychiatric disorder (schizophrenia: odds ratio = 1.1~1.2), a large sample size (typically, thousands of subjects) is required. The amount of neuroimaging data is also increasing. In VBM analysis, hundreds of thousands of voxels are analyzed. To correct for multiple comparisons in neuroimaging analyses, a critical statistical threshold is used, such as the family-wise error rate (FWE) and the false discovery rate (FDR) methods.

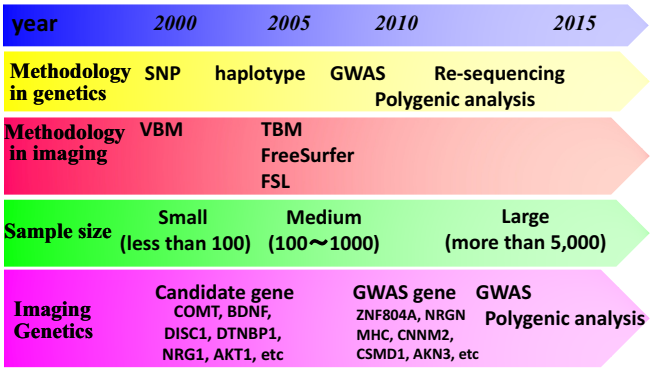

Fig. (3). Advances in imaging genetics. SNP: single nucleotide polymorphism, GWAS: genome-wide association study, VBM: voxel-based morphometry, TBM: tensor-based morphometry, FSL: FMRIB's Software Library.

Stein *et al*. attempted to perform a voxelwise genome-wide association study using the ADNI cohort (n=740), but no variant met the strict significance criterion [58]. In future imaging genetics, the association analysis of large amounts of data will require a new method for data reduction and an increase in the power to detect the signal of small effects. Two challenging works were reported in which multivariate parallel independent component analysis (ICA) and a random field theory were used [76, 77], but further development of these new methods is required.

Although the heritability of brain measures is high, even the most associated common genetic polymorphisms are individually expected to explain less than 1-5% of the variation in the most heritable brain measures [72]. Therefore, a large sample size is required and might be achieved *via* collaborative efforts, such as the ENIGMA Consortium [60]. A large sample size achieved through international collaboration and new methods might overcome the difficulty in detecting a true signal of a small effect size in the near future; however, another challenge to achieving the aim of imaging genetics remains. Most genetic variations found by GWAS are located in regions where the functional consequences of the variants are unknown. It is currently difficult to determine the function of a genetic variant, but innovation in this research area is anticipated. Future advances in imaging genetics will contribute to elucidating the pathology of psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder.

ABBREVIATIONS

ADHD = Attention deficit/hyperactivity disorder

AKT1 = v-akt murine thymoma viral oncogene homolog 1

ANK3 = Ankyrin 3

BDNF = Brain-derived neurotrophic factor

CACNA1C = Calcium channel, voltage-dependent, L type, alpha 1C subunit

CaMKII = CaM-dependent protein kinase II
CCDC68 = Coiled-coil domain containing 68
CNNM2 = Cyclin M2
COMT = Catechol-O-methyltransferase
CSMD1 = CUB and Sushi multiple domains 1
DISC1 = Disrupted-in-Schizophrenia 1
DLPFC = Dorsolateral Prefrontal Cortex
DTNBP1 = Dystrobrevin binding protein 1
FDR = False discovery rate
FWE = Familywise error rate
GWAS = Genome-wide association study
ICA = Independent component analysis
MHC = Major histocompatibility complex
MIR137 = Micro RNA 137
MMP16 = Matrix metallopeptidase 16
MRI = Magnetic resonance imaging
NAA = N-acetyl aspartate
NMDA = N-methyl-D-aspartate
NRG1 = Neuregulin-1
NRGN = Neurogranin
NT5C2 = 5'-nucleotidase, cytosolic II
ODZ4 = Odd Oz/ten-m homolog 4
SNP = Single nucleotide polymorphism
SYNE1 = Spectrin repeat containing, nuclear envelope 1
TRIM26 = Tripartite motif-containing protein 26

CONFLICT OF INTEREST

None of the authors have biomedical financial interests or potential conflicts of interest to report.

ACKNOWLEDGEMENTS

This work was supported by research grants from KAKENHI, 22390225-Grant-in-Aid for Scientific Research (B), 23659565-Grant-in-Aid for Challenging Exploratory Research and Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network) from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) as well as the Japan Foundation for Neuroscience and Mental Health.

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Received: March 22, 2014 Revised: December 20, 2014 Accepted: January 17, 2015