Aging Brain and Cognitive Intervention — The Role of Neuroimaging and Neuroengineering in Geriatrics and Gerontology

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Abstract: In this review, we focus on the role of functional magnetic resonance imaging (fMRI) to seek solutions for cognitive problems in the aging brain. fMRI enables not only visualization of the brain activities but also evaluation of neural integrity status under various physiological and pathological conditions. It is assumed that age-related hyperactivation represents potential cognitive decline leading to neural compensation. The observation that this hyperactivity was decreased after cognitive rehabilitation in older adults is compatible with this hypothesis, suggesting recovery of neural efficiency. fMRI is also applied to evaluate the risk of falls, which is a serious problem for older adults. Significant associations between brain activation with change in the risk for falls have been pointed out. Advances in fMRI, especially real-time fMRI for biofeedback and brain-computer interface, will further reveal neurophysiological basis of behavioral changes in older adults and contribute to their risk assessment. Neuroimaging is nowadays an important tool in neuroengineering not only for diagnosis but also for cognitive intervention in geriatrics and gerontology.

Keywords: Aging, Brain, functional Magnetic Resonance Imaging (fMRI), Neurorehabilitation, Real-time fMRI, Brain Computer Interface (BCI)

I. Introduction

Since the development of functional magnetic resonance imaging (fMRI) by Ogawa et al. [1], cognitive brain research has exponentially progressed. This non-invasive technique has been applied in various fields of medical and human sciences, contributing to the advancement of neuro-engineering. One such field is neurorehabilitation [2]. Not only conventional fMRI methods [3], but also real-time fMRI techniques [4] to enable biofeedback performance have been developed for clinical applications [5]. Nowadays, fMRI based neural network analysis is a powerful tool to extract the status of the aging brain [6, 7]. fMRI as well as EEG are also used to examine the validity of brain-computer interface (BCI) for cognitive neurorehabilitation [8, 9]. In this review, we focus on the role of fMRI to seek solutions for the cognitive problems in older adults as a neuroengineering tool.

II. Age-related changes of brain activation

It is known that various cognitive tasks, including motor tasks, demonstrate augmented activation in the frontal or parietal regions in older adults [10]. This age-related hyper-activation (ARHA) based on the increased amplitude of the blood oxygen level-dependent (BOLD) signal has been of interest, since it might be related to the potential risk of cognitive decline. To address this issue, longitudinal studies have been conducted as summarized below, however, its physiological basis has not been fully understood. The hemodynamic response function (HRF) of BOLD signal is principally formed as the result of complex interaction among regional cerebral blood flow (rCBF), cerebral blood volume (CBV) and oxygen consumption (CMRO₂) [11]. Considering the elongated reaction time or lower performances in older adults, it can be assumed that ARHA may be representing the increased demand for cognitive processing as the result of neuronal loss and decline of functional connectivity in the neuronal circuit, although it will be difficult to directly separate the outcome of these two different mechanisms.

One hypothesis to explain the mechanism of ARHA is demand reservation balance model. It is known that the extent of ARHA depends on the kind of task administered [12]. The activation in the primary visual area (V1) observed by checkerboard stimuli mostly depended on the decreased % BOLD signal change in older subjects, while no such age-dependent change was detected by picture viewing or prompting of a letter. Activation in the higher visual-associated areas was augmented in the older subjects by picture viewing in the same group. In the hand gripping experiment paced by viewing of pictures showing hand shapes, activations in the higher visual areas (BA19/7/39) were significantly augmented in the older subjects and depended on the BOLD waveform change rather than its amplitude. This may be representing that age-related changes resulted in more demand to process visual instructions in the visual pathways. These observations may suggest that the age-related change in brain activation may depend on the demand-reservation balance among 1) the task design and demand, 2) decline of neuronal and vascular systems and 3) functional compensation supported by the local and associated cortex. The results of hypercapnia manipulation are compatible with this hypothesis [13, 14].

The relationship between the risk of cognitive decline and ARHA has been investigated in several longitudinal studies. One early study reported ARHA in the subjects who
demonstrated cognitive decline two years later [15]. Several studies supported this view that augmented brain activation is associated with the onset of cognitive decline [16-18], while decreased activation followed by cognitive decline was also demonstrated in other studies [19-21]. The contradiction between these two results may be explained by different timing of observation in the cognitive decline course, different brain regions of interest which may depend on the task design or psychological tests employed to evaluate behavior [22, 23].

III. Action control and risk of fall

Falls have been an important topic in geriatrics since it is often injurious [24, 25]. Injuries of older adults induce functional reduction and decrease in autonomy. It was suggested that association between cognitive impairment and lower limb function in older adults might be an indicator for the risk of falls [26, 27]. There have been many epidemiologic works of falls and their prevention [28-30], and cognitive risk factors of fall have been pointed out [31, 32]. The main part of the neuronal circuit for motor execution consists of primary and higher motor areas (BA4/6) in the frontal lobe [33] where many higher cognitive functions are coordinated. Since visual cue was frequently used as the pacer for motor performance, the involvement of the visuo-motor network has been demonstrated in many sources of literature. This is reasonable as visual information processed in various ways is often used in the execution of human actions involving motor performances. The central executive system mainly located in the medial frontal lobe is also important for motor performance. Especially, the executive function involving response inhibition [34] and set-shifting [35] have been associated with cognitive risk factors for falls.

It is not difficult to deduce that cognitive decline may increase the risk of falls. Although it is very difficult to design a model to directly evaluate fall risk using fMRI, several neuroimaging approaches to investigate the cognitive vulnerability to falls have been conducted [36-39]. Eriksen Flanker task (EF task), which requires selective attention and conflict resolution, was used to explore the neuronal basis in the following studies. The HRF in the right posterior cerebellum was significantly reduced in older adults with a recent history of falls compared with non-fallers while performing the EF task [36]. Significant associations between the activation in frontal lobe towards the insula, and cingulate / paracingulate gyrus with change in physiological falls risk was detected in an observation over a 12-month period [37]. The activation in the medial frontal gyrus, playing an important role in motor planning, was decreased in fallers, providing evidence that the prefrontal cortex might play a central role in falls risk in older adults [39].

Another fMRI approach to explore falls is resting state network (RSN) analysis [38]. RSN can be detected by recording the BOLD signal without performing an explicit task. The subject is instructed to do nothing and rest, but not fall asleep, during the session. The significant signal components are detected by using functional connectivity analysis methods. It is assumed that RSN represents unconscious and automatic cognitive processes to manage memories or modulate sensory and motor systems. Age-related differences in activation for RSN have been observed [40, 41] and the decrease of connectivity in default mode network (DMN) has been reported to be correlated with structural and cognitive decline [42]. The possibility of disrupted functional connectivity was proposed as a potential mechanism for falls [38]. Less connectivity between the primary motor sensory network (SMN) and frontoparietal network (FPN) during rest was significantly associated with greater decline in both cognitive function and mobility over a 12-month period. It was suggested that an episode of multiple falls may indicate sub-clinical changes with increased risk for subsequent cognitive decline [38].

IV. Real-time functional MRI

Real-time functional MRI [4] is another fMRI-based technique that could play an important role in evaluating and enhancing action control of older adults. Using this technique to detect brain activations in almost real-time, neurofeedback training where participants are trained to control the on-going activity of a selected brain region can be performed. Effective control of a brain region's activity has been shown to translate to changes in behavior (e.g. controlling activation in the dorsal anterior cingulate cortex reduced pain perception [43]).

Real-time fMRI could also be used to enhance learning. Yoo and colleague [44] used real-time fMRI to time the presentation of novel scenes to-be-learned either during "good" or "bad" learning brain state. They showed increased or decreased learning depended on the brain state during which the stimuli were presented. Coupled with machine learning algorithms such as support vector machines, real-time fMRI has also been used to identify different brain states in real-time [45].

In older adult population, neurofeedback training could be used to augment or possibly restore function to brain regions that showed significant reduction in activation such as regions involved in action control. Providing real-time feedback of one's brain state during cognitive training could also potentially enhance cognitive training. Evaluation of spacial attention, gravity or body balance perception, recognition of body representation based on sensory feed back in real time may be a useful tool to address and possibly minimize age-related risk of falls.

V. Cognitive rehabilitation

In order to maintain quality of life, development of interventions to delay cognitive decline due to aging would be beneficial to older adults. Cognitive training intervention is one of the promising approaches to counter cognitive decline [46]. As such, a lot of studies have been conducted to examine effectiveness of the cognitive training interventions on older adults [47], and even cognitive interventions based on video games, so-called "brain training", have been studied extensively and attracted public attention [46, 48]. In fact, several computer software for brain training are available on the web, PCs, or smartphones, such as Lumosity (www.lumosity.com), CogniFit (www.cognifit.com), and Cogmed (www.cogmed.com).

The theoretical framework supporting cognitive plasticity behind the cognitive training interventions is a well-known
theory called Hebbian learning theory [49]. According to this theory, when a group of neurons fire together, the connection between them gets stronger. Thus, if particular brain regions are repeatedly activated during a course of the cognitive training, brain sub-network associated with the trained task would form stronger associations, resulting in improvement of cognitive functions involved in the task.

A major question here is an extent to which the improvement of cognitive performance would be transferred. In other words, even when learners improve their performance in a specific memory task, it may just indicate that they obtained some tips about performing the task and there may be no improvement in their memory capacity at all. Although it is likely that learners improve their performance in the trained task, what most people expect from the cognitive training is improving general cognitive functions useful in daily life. Such transferability of training-related performance gain has been examined extensively on several intervention approaches [50]. As aging is typically associated with a decline in cognitive domains such as memory, decision-making, and cognitive control, and degradation in associated brain regions such as prefrontal cortex, hippocampus, and basal ganglia [47], working memory training regimes, in particular, which require an engagement of a basic executive function called ‘updating’ [51], are likely to be beneficial to older as well as young people. Although several studies have shown far transfer effect from such working memory training to untrained tasks beyond task-specific performance in young participants [52], its generalizability still remains controversial [53], and such far transfer effect may be restricted in older adults (e.g., [51, 54]). However, a number of studies have successfully shown far transfer effects of working memory training in older participants as well (e.g., [55, 56]).

Due to the inconsistent findings in transferability of working memory training in older adults, the question regarding the circumstance in which far transfer effects are possible is raised [57]. Herbert et al. argued that training procedures targeting executive control, use of attention to enhance encoding, speed-of-processing training to overcome response conservatism, or conscious cognitive control may have more chance for far transfer [58]. In fact, recent evidence has shown that transfer effects are more likely when training regimes engage higher-level executive control processes [50] and transfer of training gain can occur only when the trained task and the transfer task engaged common cognitive processing and brain regions [51].

In order to understand what the cognitive training is actually doing, it is of great importance to investigate training-induced changes in neural substrates. A lot of studies have demonstrated modulations of brain activation induced by working memory training [for review, 52, 59]. In older adults, some studies have shown decreases in frontoparietal BOLD activation patterns along with increases in working memory performance through working memory training [51, 57, 60] or a dual-task training [61], suggesting an increase in neural efficiency. Although transfer effect from trained task to untrained tasks seems to be limited to cognitive functions engaged in trained task and such transfer effect may be more difficult in older adults [51], individual difference in cognitive abilities may be an important factor when considering gains of cognitive training and transfer effects [48]. The memory-attention network [60] or the frontoparietal WM network [57] are found to be associated with individual difference in behavioral training outcome, suggesting that adaptive control of cognitive training contingent on cognitive states of individuals can boost the training-related gains.

VI. Brain-computer interface

Until recently the concept of using BCIs for brain training of older adults to improve their motor skill and performance has not attracted much attention due to technical limits of the EEG measurement and processing in real-world environments. A BCI is a tool that converts signals recorded from the user’s brain into controls signals for different applications. Most BCI systems are based on one of the following methods: P300; steady state visually evoked potentials (SSVEP) and event--related desynchronization (ERD) [62-64]. In recent years, most of the BCI applications developed were for communication and control [65, 66]. However, recently works have adapted BCI technology for rehabilitation, also called neuromodulation or functional improvement. Different groups have begun exploring BCIs to treat symptoms of autism, psychopathy, and attentional disorders. [67, 68]. BCI for neurorehabilitation involves the recording and decoding of local brain signals generated by the patient, as he/she tries to perform a particular task or during a mental imagery task. The main objective is to promote the recruitment of selected brain areas involved and to facilitate neural plasticity. While the technology used for motor rehabilitation of patients i.e. stroke patients and aging “healthy” population is the same, the protocols and techniques are not.

A good example of how BCI technology can play an important role in motor and cognitive plasticity is in the use of this technology to improve mobility of stroke patients. Prasad et al. [69], in a cohort of patients, combined physical practice with motor imagery (MI) or post stroke neurorehabilitation and measured significant improvement. However it is not clear if the improvement was due to the neurofeedback, as studies with only MI have also shown functional improvements post-stroke. Several teams have attempted to clarify this question in a series of publications [70, 71]. Their conclusions clearly indicate that only contingent feedback on kinesthetic motor imagery leads to activations in the targeted motor regions. It facilitates adaptive neural plasticity to improve motor functioning post-stroke, emphasizing the promise of BCI-MI as a rehabilitation strategy post-stroke.

Lastly, research is being undertaken into the application of BCI systems oriented towards performing mental tasks to boost users’ cognitive capacities. The assistive applications using BCI systems are based on motor images and P300 potentials similar with those for stroke patients. These applications will allow various different cognitive processes to be trained and a multitude of heating and air-conditioning devices, lights, entertainment (TV, DVD, musical equipment, etc.) and communication devices (telephone) to be controlled [72].

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VII. Conclusion

As we have reviewed in this article, neuroimaging is becoming an important tool in neuroengineering for geriatrics and gerontology. Not only it reveals the neuronal basis of the aging brain, but also it can be applied to assess falls risk and transfer effect of cognitive intervention. The observation that brain activation was decreased after cognitive rehabilitation in older adults is compatible with the hypothesis of neural compensation, suggesting recovery of neural efficiency. The risk of falls is a serious problem for older adults. Significant associations between brain activation with change in the risk of falls have been pointed out, suggesting that neuroimaging will be potentially useful to evaluate the risk. Recent developments in BCI have shown great promise for this technique to modulate neuroplasticity in healthy and clinical populations. Advances in fMRI techniques, especially real-time fMRI for biofeedback, will further reveal neurophysiological basis of behavioral changes in older adults, and contribute to their risk assessment and support the development of technologies to enhance cognitive interventions. Integration of neuroimaging with a wide range of behavioral measurements will powerfully enhance BCI therapy to improve the quality of life for older adults [73].

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References
