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RESEARCH ARTICLE

Cross-modal plasticity after auditory working memory training in stroke

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Abstract

The present study investigated cross-modal plasticity after a course of auditory working memory training. Two clients with stroke completed auditory *n*-back tasks (1-,2- and 3-back) in a graded manner for a total of 20 hours over a six-week period. Neural activations on auditory and visual *n*-back tasks (1- and 2-back) were assessed before and after training. The two clients demonstrated different patterns of results. The client with intact fronto-parietal network demonstrated substantial improvement on *n*-back performance. Additionally, the neural activation in the fronto-parietal network subsided after training in both the auditory and visual *n*-back tasks, and there were extensive activationsin the cerebellum. In contrast, the client with a largearea of damage in the fronto-parietal network showed no evidence of frontal and parietal activation before training, and the performance of the *n*-back tasks was comparatively poor and was mainly supported by temporal lobe activities. The results suggest that effective cross-modal transfer after stroke require an intact fronto-parietal network. Other regions like the cerebellum might also contribute to cross-modal transfer. Future larger scale study is recommended to disentangle individual differences in neural activity after training.

INTRODUCTION

About half of stroke survivors have difficulty in daily activities due to cognitive deficits (Patel, Coshall, Rudd, & Wolfe, 2003). Rehabilitation programs that address cognitive impairments have been found to remediate a broad range of cognitive components including attention, memory and executive function (Leung et al., 2010; Rees et al., 2007; Cicerone et al., 2011). Recent reviews have found that cognitive training using auditory materials is beneficial for stroke patients who have visual-spatial neglect (Cicerone et al., 2011). However, it is largely unclear what mechanisms underlie the observable improvements or transfer of skills after cognitive training.

Using functional magnetic resonance imaging (fMRI), recent studies have found a robust set of brain regions, including the frontal, parietal and temporal gyri, responsible for processing sound content in auditory working memory (Alain et al., 2001; Leung & Alain, 2011). Additionally, most working memory tasks such as *n*-back tasks (i.e., comparing a stimulus in the current trial with *n* trial(s) back) have been found to activate the bilateral fronto-parietal neural network (Wager and Smith, 2003; Owen, McMillan, Laird, & Bullmore, 2005).

Research focusing on the investigation of the effects of auditory working memory training is rare. Using visual modality, most studies reported a decrease in neural activation in the fronto-parietal network after working memory training (Garaven, Kelley, Rosen, Rao, & Stein, 2000; Landau, Garavan, Schumacher, & D’Esposito, 2007). This network consists of the inferior, superior and middle frontal gyri, and the inferior and superior parietal lobes.Others found an increase of neural activation in the middle frontal gyrus and the inferior parietal lobe after training (Olesen, Westerberg, and Klingberg, 2004). According to Kelly and Garavan (2005), activation decreases reflect improved neural efficiency in performing the task while activation increases indicate an expansion of activity for improving task performance.

An important consideration in training studies is whether the training effect is domain-specific or process-specific (Westerberg & Klingberg, 2007; Olesen et al., 2004). Domain-specific effect means training on one modality (e.g., auditory) improves performance in the same modality (e.g., auditory) and shows positive relationships between task accuracy and neural activity (Moore, Cohen, & Ranganath, 2006). Process-specific effect means training on one modality (e.g., auditory) improves performance in a different modality (e.g., visual), and is demonstrated by reduced activation in the fronto-parietal network (Garavan et al., 2000; Brehmer et al., 2011). Some studies found that reduced activation in the fronto-parietal network and faster processing speed in practice tasks were crucial for transfer (Sayala et al., 2006; Kelly & Garavan, 2005; Takeuchi et al., 2011). Hence, by using a cross-modal training design, one can examine these training effects on stroke patients in a controlled way.

Schneiders, Opitz, Krick, and Mecklinger's study (2011) is among the few that have investigated cross-modal plasticity in healthy adults. They found performance improvement and a reduction of neural activities in the fronto-parietal network, a pattern consistent with the process-specific training effect. However, there has not been study examining cross-modal plasticity in patients with brain lesion.

In the past, training studies were most often done using repeated practice approach, with an assumption that repeated practice of a task over an extended period could lead to performance improvement (Li et al., 2015). Previous studies found that three to six weeks of task practice was optimal for promoting skill transfer to untrained tasks (Klingberg, 2010).

This study aimed to investigate cross-modal plasticity following a course of auditory working memory training in patients with stroke. We hypothesized that training would modulate neural activities in the fronto-parietal network differently in patients with different levels of brain lesion in the network.

METHOD

Two patients with similar demographic backgrounds were recruited to the study. They were bilingual and right-handed and had no documented history of any other neurological or psychiatric conditions. Both of them were not having any rehabilitative treatments at the time of the experiment.

Case history

Client 1 was a 38-year-old man who suffered a right-sided cerebral vascular accident (CVA) involving the middle cerebral artery (MCA) nineteen years prior to the study. Magnetic resonance imaging (MRI) showed restricted diffusion to the right parietal lobe, superior right frontal lobe and the anterior portion of the anterior medial frontal lobe, and enlargement of the lateral ventricles. Many years ago, he completed a course of rehabilitativeprogramfor improving his motor skills but did not receive any training for cognitive remediation. He had completed an undergraduate degree and was working full time in a business firm. He continues to report cognitive deficits that are noticeable during work and home life.

Client 2 was a 37-year-old woman who sustained a right-sided CVA involving the MCA three years ago. She also hadan episode of cerebral infarction in the brain-stem duringher hospitalized for her stroke. MRI detected small areas of lesion at the right superior and medial frontal gyri and the precentral gyrus. Two years ago, she completed a course of cognitive training in an outpatient clinic. She had completed an undergraduate degree and was working full time in a private company. She feels fatigue easily and continues to have difficulties with memory and concentration that affect her performance at work.

General procedure

Participants provided written consent during the intake interview. They were screened to ensure safety for fMRI procedures according to the guidelines from the Peter S. Allen MR Research Centre at the University of Alberta (UA). Participants completed pre-training assessments that included neuropsychological tests, auditory and visual *n*-back tasks, and a self-report questionnaire on perceived cognitive deficits. An audiogram was performed to ensure they had pure-tone thresholds less than or equal to 20 dB hearing level (HL) at a frequency range between250 and 4000 Hz in both ears.After that, participants performed pre-training fMRI scanning on both auditory and visual *n*-back tasks, and started the training at home using a laptop provided by the researchers. A research assistant contacted them every week to provide feedback ontheir performance. Within one week after the training, participants completed post-training assessments on the tests and fMRI they did before the training. The study was approved by the Research Ethics Board at UA.

Auditory and visual *n*-back tasks

Stimuli were letters and digits. For auditory *n*-back tasks, the stimuli were recorded by a research assistant (average root mean square power of 18.68 dB) (Leung, Ng, Yuen, Dixon, & Kim, 2014). The stimuli were presented in a volume of 80 dB through a pair of headphones. For visual *n*-back tasks, the stimuli were presented in white on a black background, sustaining at a visual angle of 16 degrees. The tasks were presented using E-Prime2.0 (Psychology Software Tools). Each task block consisted of 30 stimuli, each presented for one second followed by a 1-second pause. For 1-back tasks, participants pressed a button when the current stimulus was identical to the one before. For 2- and 3- back tasks, participants pressed the button when the current stimulus was identical to the one in two trials or three trials back, respectively.Before and after training, participants performed both the auditory and visual *n*-back tasks (n = 1 and 2). During training, participants performed only the auditory *n*-back task (n = 1, 2 and 3).

Training program

The training occurred five days per week for six consecutive weeks. Each day participants completed four 10-minute tasks, resulting in a total of 20 hours of task practice in the entire training program. The four tasks were organized such that the distribution of 1-, 2- and 3-back tasks was assigned in a graded manner. Participants were required to achieve on average 65% hit rate on all tasks in a week, or they would need to repeat the same schedule in the other week. This training approach controlled the amount of task exposure while allowing the progression of task difficulty in the training (Leung et al., 2014; Li et al., 2008).

fMRI scanning

Participants performed auditory and visual *n*-back tasks (1-back and 2-back) during fMRI scanning before and after training. There were three runs for each of the auditory and visual tasks. Each run consisted of six 42-second task blocks interleaved with six 30-second rest blocks. Each task block contained a 2-second spoken instructionto indicate the type of task (1-back or 2-back) and twenty 2-second trials (600 ms for stimulus + 1400 ms for pause). Participants responded to targets by pressing a button with the right hand. Participants completed one modality before performing the other.

Participants performed fMRI scanning in the Peter S. Allen MR Research Centre at UA. A 1.5-T Siemens MRI system with a standard birdcage head coil were used. Structural T1 weighted anatomical volumes were obtained (axial orientation; TR=2080 ms; TE=4.38 ms; FOV=256 mm; slice thickness=1 mm). Functional T2* images were obtained using EPI acquisition (TR=1950 ms; TE=40 ms; flip angle=90°; FOV=256 mm; matrix=64×64; thirty-six 4-mm axial slices covering the whole brain). There were altogether six functional runs with each lasted 7 minutes and 42 seconds.

Analysis of *n*-back performance

For each*n*-back task, a d-prime (*d'*) index was calculated using the formula $d' = Z_{\text{hits}} - Z_{\text{false alarms}}$, where Z is the transformation of the two distributions allowing for comparison of measures with different ranges of absolute values (Macmillan & Creelman, 1991). The *d'* provides a single index to analyze the performance of *n*-back tasks across time (Haatveit et al., 2010). A value of 0 would indicate thatboth the hit and false alarm rates were 50%. A positive *d'*would indicate higher than chance performance, and a higher *d'* would indicate more accurate task performance (Leung et al., 2014).

Cohen's *d* statistic was used to measure the extent of performance change in the training (Cohen, 1988). Cohen's *d*was calculated for each of the auditory and visual *n*-back tasks using the formula, i.e., Cohen's $d = (\text{Mean}_{A2} - \text{Mean}_{A1})/\text{SD}_{A1}$, where A2 and A1were post- and pre-training testing, respectively (Beeson & Robey, 2006). An average Cohen's *d* was calculated to reflect the overall effect size of training.

Analysis of fMRI data

Neuroimaging scans were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, UK). For each run, the first five images were discarded to remove artifacts. All remaining images underwent slice timing, realignment, motion correction, co-registration, normalization, and smoothing (Leung et al., 2014). The preprocessed images were modeled using a general linear model (GLM). Separate regressors were appliedfor sustained (activity spanning the entire duration of the task blocks) and transient activities (activity unique to the hit responses on targets) in each of the three experimental factors (modality: auditory and visual; load: 1-back and 2-back; time: pre- and post-training). The modeled data were high-pass filtered to remove low-frequency drift.

The analysis was performed separately for each participant. All contrasts were performed on sustained activities to minimize neural activations resulting from motor responses. A first-level analysis produced an *F* contrast for examining the interaction between modality, load, and time, and *T* contrasts for comparison within experimental factors. Technical details could be found in Leung et al.'s study (2014). Significant brain activations from the *F* contrast were examined on the *T* contrasts that compared neural activation between the pre- and post-training sessions on each of the two modalities and load levels. Only activations that had a cluster size greater than

196 μl were regarded statistically significant and were reported. Activation maps were displayed using MRIcron (http://www.sph.sc.edu/comd/rorden/mricro.html), and brain regions were labeled usingthe Automated Anatomical Labeling (AAL) system (Tzourio-Mazoyer et al., 2002).

RESULTS

N-back performance in training

Before and after training, client 2 had much greater improvements than client 1, especially on 2-back tasks in both modalities (Table 1). The average Cohen's *d* for client 2 were comparable to that of healthy adults and brain damaged patients in other studies (Robey, Schultz, Crawford, & Sinner, 1999; von Bastian, Langer, Jancke, & Oberauer, 2013). During training, only client 2 showed gradual increase in performance across weeks (increasing *d'* and faster reaction time).

fMRI results

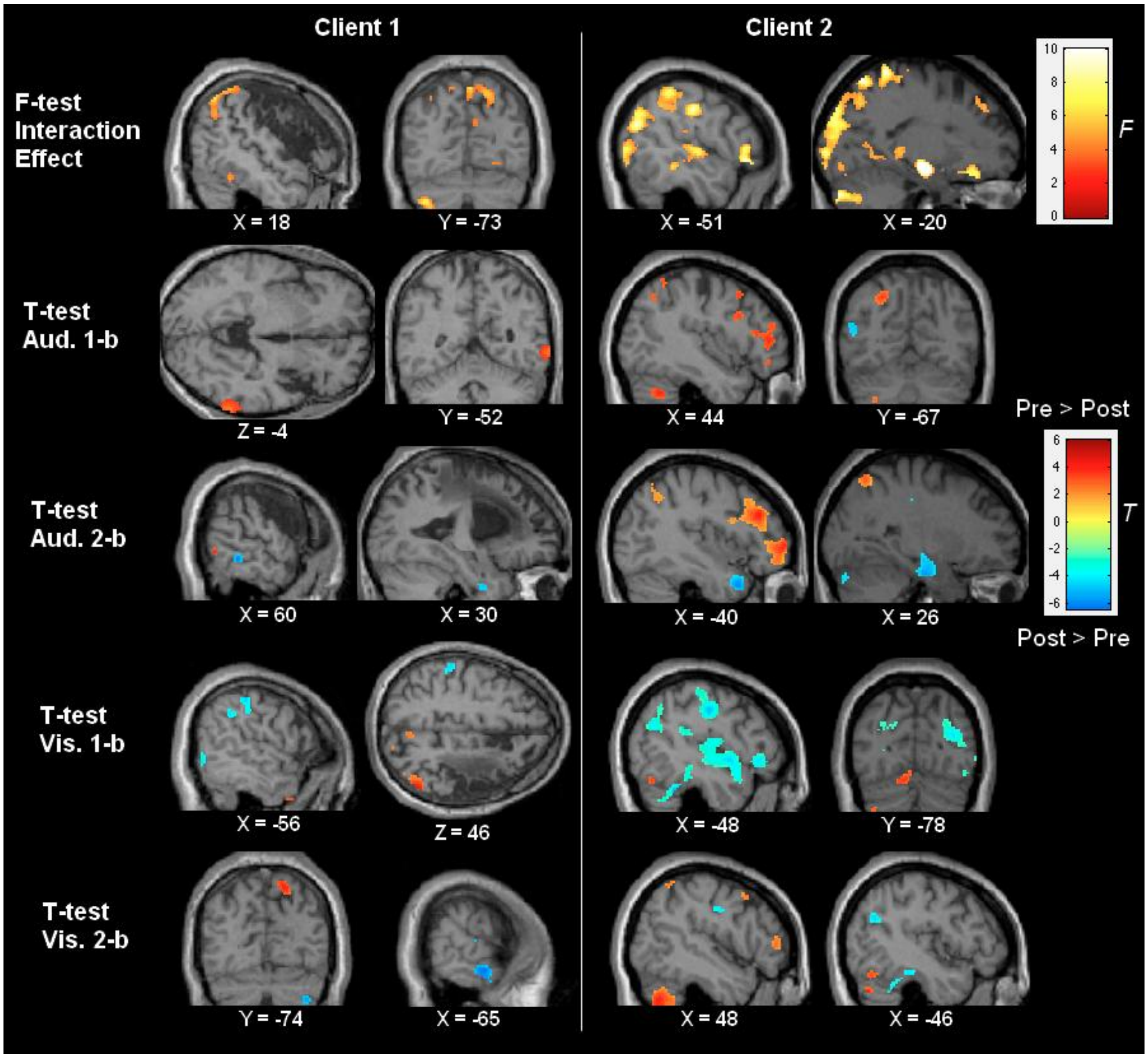
Both clients showed over 90% of hit rate in both the 1-back and 2-back tasks during scanning. Figure 1 shows the results of *F*and *T*contrasts for clients 1 and 2. Overall, client 2 demonstrated more extensive interaction effects than client 1, especially in the fronto-parietal network. For client 1, there were significant activations in the parietal regions for the visual tasks, but no activationwas found in the frontal regions for all tasks. For client 2, the activations in the fronto-parietal network subsided after training, and there were extensive activations over the cerebellum for the visual tasks in the post-training testing.

Table 1. Cohen's *d* of the auditory and visual *n*-back tasks measured before and after training.

	Client 1				Client 2			
	Auditory		Visual		Auditory		Visual	
	1-b	2-b	1-b	2-b	1-b	2-b	1-b	2-b
Mean A_1^*	3.32	3.19	4.51	2.92	4.18	3.04	2.89	2.04
Mean A_2^*	3.43	3.05	3.64	4.24	4.23	3.90	4.03	3.88
Mean A_2 – Mean A_1^*	0.11	-0.14	-0.87	1.32	0.05	0.86	1.14	1.84
SD A_1^*	0.42	0.62	0.85	0.49	0.79	0.11	0.74	0.48
Cohen's *d*	0.27	-0.23	-1.02	2.68	0.06	7.90	1.54	3.83
Average Cohen's *d*	0.02		0.83		3.98		2.69	

Note: Mean A_1 reflects the average of task performance in the pre-training testing and mean A_2 reflects the average of task performance in the post-training measurement. Average Cohen's *d* reflects the weighted mean of 1-back and 2-back task performance for the pre-training and post-training testing. 1-b = 1-back task; 2-b = 2-back task; all values represent *d'*.

Figure 1. Activation maps showing the results of the *T*and *F*contrasts of the two clients.



Note: All activations are significant at $p< 0.005$ and cluster size> 196 μl. Only true activations are listed. Activations are overlaid on the clients' anatomical images.

DISCUSSION

The present study investigated cross-modal plasticity in two adults with stroke. client 1 showed minimal improvement on auditory and visual *n*-back tasks while client 2 demonstrated substantial improvement on all *n*-back tasks and behaviorial tests. fMRI results indicated that only client 2 had substantial activation in the fronto-parietal network before training, which subsided after training. Client 2 also had extensive activations in multiple cortices and the cerebellum in the untrained visual tasks during the post-training testing. The results showed that effective cross-modal transfer in stroke seemed to require an intact fronto-parietal network. Post-stroke rehabilitation might play a key role in restoring the network. Other regions like the cerebellum and parahippocampus might also contribute to cross-modal transfer and cognitive recovery.

In this study, cross-modal plasticity was best demonstrated by substantial improvement in visual 2-back performance in client 2. A closer look at the neural activation on the visual 2-back task found activation decrease in frontal and parietal regions in the post-training testing. The reduction of neural activation was consistent with previous working memory training studies on healthy young adults or patients with stroke (e.g., Westerberg et al., 2007; Garaven et al., 2000), which was thought to be related to increased neural efficiency and the use of more precise neuronal and functional circuits (Kelly & Garaven, 2005; Takeuchi et al., 2010). Such an improvement in neural efficiency probably promoted a favourable condition for cross-modal transfer to take place, which increased the client's ability to succeed in other cognitive tests and perception of cognitive gains. For client 1, there was no evidence of frontal and parietal activation before training, and the performance of the *n*-back tasks was comparatively poor and was mainly supported by temporal lobe activities. It was suggested that the lack of efficient use of the fronto-parietal network had negatively impacted working memory performance, which reduced the likelihood of successful learning and transfer.

An interesting finding was that client 2 had extensive activations in the cerebellum in untrained visual tasks after training. Cerebro-cerebellar circuits have been found to engage in the simultaneous processing of auditory and visual information, which supports the integration of cross-modal information (Petacchi, Laird, Fox, & Bower, 2005; Kirschen, Chen, and Desmond., 2010). The cerebellum, especially lobules VI and crus 1 and 2, are also related to the maintenance and manipulation of information (Hayter, Langdon, and Ramnani, 2007). For client 2, the extensive cerebellar activation was possibly resulted from improved neural connectivity in the cerebro-cerebellar circuit which connected over a large network of areas involving the frontal, parietal, temporal and occipital gyri. It was worth noting that client 1 also showed activation in the cerebellum in the visual 2-back task after training. However, the activation appeared to be a compensatory mechanism as client 1 had a large area of cortical damage over the superior frontal and precentral areas. Previous study has shown that the cerebellum is strongly activated in cognitive tasks when cortical regions are damaged (Timmann & Daum, 2007).

Overall, client 1 showed minimal transfer effects and neuroplastic changes in untrained visual tasks, which could be attributed to several clinical factors. First, client 1 had a large extent of brain damage that destroyed the fronto-parietal network. Second, client 1 had a much longer post-stroke duration than client 2. Third, client 1 received movement therapy for his motor deficits butdid not receive any therapy for his cognitive impairment after his stroke many years ago. Our results suggest that clinicians should consider early cognitive remediation to help restore or rewire neural networks in order to increase the likelihood of cognitive skill retention and transfer (Cicerone et al., 2011; Gillespie et al., 2014). The results also consolidated previous researchthathighlighted the importance of intact white matter tracks, especially the fronto-parietal network, for cognitive recovery in stroke (Kliper et al., 2014).

There were some limitations in this casestudy. First, the post-stroke duration and gender was not controlled due to the difficulty to find suitable participants. Second, time of day of training and motivation level of clients, which might influence training outcome, was not controlled. Therefore, the results should be interpreted with a great deal of caution. In future studies, a larger sample is needed to disentangle the effect of individual differences on the neuroplastic change.

CONCLUSION

Contrasting the results of two clients, we found that effective cross-modal transfer in stroke seemed to require an intact fronto-parietal network and neural activity in the cerebellum. The results provided anew piece of knowledge in understanding the neural mechanism of cross-modal plasticity in brain lesion resulting from stroke. The results also shed light on the need for early cognitive intervention to restore the fronto-parietal network for better treatment outcome.

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REFERENCES

Aguirre, G.K., Detre, J.A., Alsop, D.C., D’Esposito, M. (1996). The parahippocampus subserves topographic learning in man. Cereb Cortex, 6(6), 823-829.

Alain, C., Arnott, S.R., Hevenor, S., Graham, S., Grady, C.L. (2001). “What” and “Where” in the human auditory system. PNAS, 98(21), 12301-12306.

Alain, C., He, Y., Grady, C. (2008). The contribution of the inferior parietal lobe to auditory spatial working memory. J Cogn Neurosci, 20(2), 285-295. doi: 10.1162/jocn.2008.20014.

Beeson, P.M. & Robey, R.R. (2006). Evaluating single-subject treatment research: lessons learned from the aphasia literature. Neuropsychol Review, 16(4), 161-169.

Brehmer, Y., Rieckmann, A., Bellander, M., Westerberg, H., Fischer, H., Bäckman, L. (2011). Neural correlates of training-related working memory gains in old age. Neuroimage, 58(4), 1110-1120. doi: 10.1016/j.neuroimage.2011.06.079.

Bridger, R.S., Johnsen, S.A.K., Brasher, K. (2013). Psychometric properties of the Cognitive Failures Questionnaire. Ergonomics, doi: 10.1080/00140139.2013.821172.

Broadbent, D.E., Cooper, P.F., FitzGerald, P., Parkes, K.R. (1982). The cognitive failures questionnaire (CFQ) and its correlates. Brit J of Clin Psychol, 21, 1-16.

Cicerone, K.D., Langenbahn, D.M., Braden, C., Malec, J.F., Kalmar, K., Fraas, M., . . . Ashman, T. (2011). Evidence based cognitive rehabilitation: Updated review of the literature from 2003 through 2008. Arch Phys Med Rehab, 92(4), 519-530. doi:10.1037/a0013659

Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences, Second Edition. Hillsdale, NJ: Lawrence Erlbaum Associates.

Garaven, H., Kelley, D., Rosen, A., Rao, S.M., Stein, E.A. (2000). Practice-related functional activation changes in a working memory task. Micro Res Tech, 51(1), 54-63.

Gillespie, D.C., Bowen, A., Chung, C.S., Cockburn, J., Knapp, P., Pollock, A. (2014). Rehabilitation for post-stroke cognitive impairment: An overview of recommendations arising from systematic reviews of current evidence. Clin Rehab, 1-9. doi: 10.1177/0269215514538982.

Haatveit, B.C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., Andreassen, O.A. (2010). The validity of d prime as a working memory index: Results from the “Bergen n-back task”. J Clin Exp Neuropsychol, 32(8), 871-880.

Hayter, A.L., Langdon, D.W., Ramnani, N. (2007). Cerebellar contributions to working memory. Neuroimage, 36(3), 943-954.

Kelly, A.M.C. & Garavan, H. (2005). Human functional neuroimaging of brain changes associated with practice.Cereb Cortex, 15(8), 1089-1102. doi: 10.1093/cercor/bhi005

Kirschen, M.P., Chen, A.S.H., Desmond, J.E. (2010). Modality specificcerebro-cerebellar activations in verbal working memory: an fMRI study. Behavioral Neurology, 23(1-2), 51-63. doi: 10.3233/BEN-2010-0266.

Klingberg, T. (2010). Training and plasticity of working memory. Trends Cogn Sci, 14(7), 317-324.

Kliper, E., Assayag, E.B., Tarrasch, R., Artzi, M., Korczyn, A.D., Shenhar-Tsarfaty, S., . . . Bashat, D.B. (2014). Cognitive state following stroke: The predominant role of preexisting white matter lesions. PLOS One, 9(8), e105461. doi: 10.1371/journal.pone.0105461.

Landau, S.M., Garavan, H., Schumacher, E.H., D'Esposito, M. (2007). Regional specificity and practice: dynamic changes in object and spatial working memory. Brain Res, 1180, 78-89.

Leung A.W.S. & Alain, C. (2011). Working memory load modulates the auditory "What" and "Where" neural networks. Neuroimage, 55(3), 1260-1269.

Leung A.W.S., Cheng, S.K.W., Mak, A.K.Y., Leung, K.K., Li, L.S.W., Lee, T.M.C. (2010). Functional gain in hemorrhagic stroke patients is predicted by functional level and cognitive abilities measured at hospital admission. NeuroRehab, 27(4), 351-358.

Leung, A.W.S., Ng, B.P.S., Yuen, J., Dixon, G., Kim, E.S. (2014). Neuroplastic changes after auditory working memory training in a patient surviving multiple strokes.J Neurosci Rehab, 1, 1-22.

Lezak, M.D. (1976). Neuropsychological Assessment. New York: Oxford University Press.

Li, S.C., Schmiedek, F., Huxhold, O., Röcke, C., Smith, J., Lindenberger, U. (2008). Working memory plasticity in old age: practice gain, transfer, and maintenance. Psychol Aging, 23(4), 731-42.

Li, X., Xiao, Y., Zhao, Q., Leung, A.W.S., Cheung, E.F.C., Chan, R.C.K. (2015). The neuroplastic effect of working memory training in healthy volunteers and patients with schizophrenia: Implications for cognitive rehabilitation. Neuropsychologia, 75, 149-162. doi: 10.1016/j.neuropsychologia.2015.05.029

Lin, Z., Tao, J., Gao, Y., Yin, D., Chen, A., Chen, L. (2014). Analysis of central mechanism of cognitive training on cognitive impairment after stroke: resting-state functional magnetic resonance imaging study. J Int Med Res, 42(3), 659-668.

Macmillan, N.A. & Creelman, C.D. (1991). Detection Theory: A User’s Guide. New York: Cambridge University Press.

Moore, C.D., Cohen, M.X., Ranganath, C. (2006). Neural mechanisms of expert skills in visual working memory. J Neurosci, 26(43), 11187-11196.

Olesen, P.J., Westerberg, H., Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. Nature Neurosci, 7(1), 75-79.

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies.Hum Brain Map, 25(1), 46-59.

Patel, M., Coshall, C., Rudd., A.G., Wolfe, C.D. (2003). Natural history of cognitive impairment after stroke and factors associated with its recovery. Clin Rehab, 17(2), 158-164.

Petacchi, A., Laird, A.R., Fox, P.T., Bower, J.M. (2005). Cerebellum and auditory function: An ALE meta-analysis of functional neuroimaging studies. Hum Brain Map, 25(1), 118-128.

Rees, L., Marshall, S., Hartridge, C., Mackie, D., Weiser, M. (2007). Cognitive interventions post acquired brain injury. Brain Injury, 21(2), 161-200.

Robey, R.R., Schultz, M.C., Crawford, A.B., Sinner, C.A. (1999). Single-subject clinical-outcome research: designs, data, effect sizes, and analyses. Aphasiology, 13(6), 445-473.

Sayala, S., Sala, J.B., Courtney, S.M. (2006). Increased neural efficiency with repeated performance of a working memory task is information-type dependent.Cereb Cortex, 16(5), 609-617.

Schneiders, J.A., Opitz, B., Krick, C.M., Mecklinger, A. (2011). Separating intra-modal and across-modal training effects in visual working memory: An fMRI investigation. Cerebral Cortex, 21(11), 2555-2564.

Smith, A. (1982). Symbol digit modalities test: Manual. United States: Western Psychological Services.

Stroop, J.R. (1935). Studies of interference in serial verbal reactions. J Exp Psychol, 18(6), 643-662.

Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., . . . Kawashima, R. (2010). Training of working memory impacts structural connectivity. J Neurosci, 30(9), 3297-3303.

Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., Nouchi, R., Kawashima, R. (2011). Effects of training of processing speed on neural systems. J Neurosci, 31(34), 12139-12148.

Timmann, D. & Daum, I. (2007). Cerebellar contributions to cognitive functions: a progress report after two decades of research. Cerebellum, 6(3), 159-162.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labelling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage, 15(1), 273-289.

von Bastian, C.C., Langer, N., Jancke, L., Oberauer, K. (2013). Effects of working memory training in young and old adults. Mem Cogn, 41(4), 611-624. doi: 10.3758/s13421-012-0280-7.

Wager, T.D. & Smith, E.E. (2003). Neuroimaging studies of working memory: A meta-analysis. Cogn Affect Behav Neurosci, 3(4), 255-274.

Westerberg, H. & Klingberg, T. (2007). Changes in cortical activity after training of working memory – a single-subject analysis. Physiol Behav, 92(1-2), 186-192.

Westerberg, H., Jacobaeus, H., Hirvikoski, T., Clevberger, P., Ostensson, M.L., Bartfai, A., Klingberg, T. (2007). Computerized working memory training after stroke – a pilot study. Brain Injury, 21(1), 21-29.