Multisensory stimulation in stroke rehabilitation

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The brain has a large capacity for automatic simultaneous processing and integration of sensory information. Combining information from different sensory modalities facilitates our ability to detect, discriminate, and recognize sensory stimuli, and learning is often optimal in a multisensory environment. Currently used multisensory stimulation methods in stroke rehabilitation include motor imagery, action observation, training with a mirror or in a virtual environment, and various kinds of music therapy. Non-invasive brain stimulation has showed promising preliminary results in aphasia and neglect. Patient heterogeneity and the interaction of age, gender, genes, and environment are discussed. Randomized controlled longitudinal trials starting earlier post-stroke are needed. The advance in brain network science and neuroimaging enabling longitudinal studies of structural and functional networks are likely to have an important impact on patient selection for specific interventions in future stroke rehabilitation. It is proposed that we should pay more attention to age, gender, and laterality in clinical studies.

Keywords: motor imagery, virtual reality

INTRODUCTION

We live in a multisensory environment and the interaction between our genes and the environment shapes our brains. The brain has a large capacity for automatic simultaneous processing and integration of sensory information, and multisensory influences are integral to primary as well as higher order cortical operations (Ghazanfar and Schroeder, 2006). Combining information from different sensory modalities facilitates our ability to detect, discriminate, and recognize sensory stimuli (Driver and Noesselt, 2008; Shams and Seitz, 2008; Gentile et al., 2011). Non-invasive brain stimulation does not only affect the targeted local regions but also activity in remote interconnected regions. Although repetitive transcranial magnetic stimulation (rTMS) cannot directly target subcortical structures, the activity in thalamus can be modulated by stimulation of parietal cortex, an observation that open up new possibilities for studies of cortical–subcortical interactions in multisensory processing (Blankenburg et al., 2008, 2010). Multisensory enhancement of detection sensitivity for low-contrast visual stimuli by sounds reflects a brain network involving not only established multisensory and sensory-specific cortex but also visual and auditory thalamus (Noesselt et al., 2010). Diffusion tensor imaging and tractography have enhanced the opportunity to study white matter tract networks and compare structural and functional connectivity in humans (Ciccarelli et al., 2008). Combining non-invasive brain stimulation with neuroimaging offers an opportunity to study causal relations between specific brain regions and individual cognitive and perceptual functions (Driver and Noesselt, 2008; Driver et al., 2009; Bolognini and Maravita, 2011; Zamora-López et al., 2011). Non-invasive brain stimulation techniques have the advantage that they can be used both as diagnostic tools and in treatment.

MIRROR NEURONS, TRAINING WITH A MIRROR, AND ACTION OBSERVATION

During intracellular recordings in macaque monkeys, premotor neurons that discharge both in association with performance of a motor task and when observing a human individual performing the same action were identified and named mirror neurons (Gallese et al., 1996). In addition to action understanding, mirror neurons have also proposed to be fundamental for imitation learning (Rizzolatti and Craighero, 2004) and for language (Rizzolatti and Arbid, 1998) and social interactions.

Activation of human primary motor cortex during action observation was first observed in a neuromagnetic study by Hari et al. (1998). In a following study on the temporal dynamics of the cortical representation for action (Nishitani and Hari, 2000), the left inferior frontal cortex, Brodmann's area (BA) 44, was activated first followed within 100–200 ms by activation of the left primary motor area (BA4) and 150–250 ms later by the right BA4. The data suggest that that left BA44 is the orchestrator of the human "mirror neuron system" and is strongly involved in action imitation. It was also shown that the reactivity of the human primary motor cortex was stronger during observation of live rather than video motor acts (Järveläinen et al., 2001).

The same motor neuron regions that are activated both when performing and when observing a movement are also activated prior to observing another persons action. This observation suggests that the mere knowledge of an upcoming movement is sufficient to excite one's own motor system, enabling people to anticipate, rather than react to, the action of others (Kilner et al., 2004). These and other studies have let to the suggestion that mirror neurons may be a product of associative learning (Catmur et al., 2009, 2011; Kilner et al., 2009a,b; Heyes, 2010). The associative learning hypothesis proposes that the mirror neurons are

not innate but plastic, and can be transformed by sensorimotor learning and experience during life (Heyes, 2010; Catmur et al., 2011). Brain imaging studies suggest that areas responding to the observation and performance of actions are more widespread in the human brain and that multiple regions that process both sensory and motor information have the potential to contribute to mirror effects.

In a recent fMRI study 20 participants observed identical actions under different instruction context. A multi-voxel pattern analysis revealed unique patterns of activation in ventral premotor cortex and inferior parietal lobule across the difference contexts. The task was either to understand the actions, to identify the physical feature of the actions, or passively observe the action. The results showed that ventral premotor and inferior parietal areas respond differently to observed actions depending on the mindset of the observer (Molenberghs et al., 2012a).

A meta-analysis of 125 human fMRI studies that met strict inclusion and exclusion criteria revealed 14 separate clusters in which activation have been consistently attributed to brain regions with mirror properties encompassing 9 different Brodmann areas. These clusters were located in areas considered to show mirroring properties in the macaque such as the inferior parietal lobule, inferior frontal gyrus, and the adjacent ventral premotor cortex, but also the primary visual cortex, cerebellum, and parts of the limbic system. The findings suggest a core network of human brain regions that possess mirror properties associated with action observation and execution, with additional areas recruited during tasks that engage non-motor functions such as auditory, somatosensory, and affective components (Molenberghs et al., 2012b).

The temporal dynamics of the brain activation during the observation of a motor act and underlie the observers capacity to understand what the agent is doing and why, has been studied with high-density EEG neuroimaging (Ortique et al., 2010). Two volunteers were presented with two-frame video-clips, the first showed an object with or without context, the second frame showed a hand interacting with the object. Visual event-related potentials were recorded time-locked with the frame showing the hand–object interaction. The results revealed four major steps (1) bilateral posterior cortical activation, (2) a strong activation of the left posterior temporal and inferior parietal cortices with almost a disappearance of activation in the right hemisphere, (3) a significant increase of the activations of the right temporal–parietal region with simultaneously co-activation of some areas in the left hemisphere, (4) a significant global decrease of cortical activity accompanied by activation in the orbitofrontal cortex. The interpretation of the authors was that the early left hemisphere involvement was due to the activation of a lateralized action observation/action execution network that mediates the understanding of the goal of object-directed motor acts (mirror mechanism), and that the successive right-hemisphere activation indicated an important role in understanding the intention of others.

Actions can be described at multiple levels including the kinematic level, the motor level, the goal level and the intention level, and there are thus multiple levels at which an observed action can be understood. The action observation network is unlikely to encode the more abstract levels of understanding such as the intention and the goal of the action (Kilner, 2011). Kilner argues that the ability to understand actions at these abstract levels is most likely encoded in the middle temporal gyrus and the more anterior regions of the inferior frontal gyrus in a ventral pathway.

That viewing the mirror reflection of movement of the unimpaired arm could improve functional recovery of the impaired (not visible) arm following stoke was first shown in a placebo-controlled pilot study by Altschuler et al. (1999). In training with a mirror, the patient's affected hand is hidden behind a mirror. Sathian et al. (2000) reported a case study using this approach to stroke rehabilitation in a patient with poor function of an arm due mainly to somatosensory deficits after stroke. Mirror therapy facilitated employment of a motor copy strategy involving bimanual movements and later "forced use" of the affected arm.

While moving the unaffected arm, that patient watches its mirror image as it were the affected arm, and viewing the mirror reflection facilitates ipsilateral motor cortex excitability (Garry et al., 2005). In 40 patients, included within 12 months post-stroke, hand function improved more after mirror therapy in addition to a conventional rehabilitation program after 4 weeks of treatment and at 6 months follow-up (Yavuzer et al., 2008). Thirty-six patients with severe hemiparesis because of a first-ever ischemic stroke in the middle cerebral artery territory were enrolled not more than 8 weeks after the stroke to an additional protocol of 6 weeks therapy 30 min a day, 5 days a week, with random assignment to either mirror therapy or an equivalent control therapy (Dohle et al., 2009). The distal functions of the arms improved more with mirror therapy. Furthermore, mirror therapy enhanced recovery of surface sensibility and stimulated recovery from hemineglect. Neither of there effects depended on the side of the damaged hemisphere. In a phase II randomized controlled trial with 40 chronic stroke patients (mean time post onset 3.9 years) motor functions improved more in the mirror than in the control groups (Michielsen et al., 2011). The improvement did not persist at follow-up, but fMRI results showed a shift in activation balance within the primary motor cortex toward the affected hemisphere in the mirror group only ($p < 0.05$).

Action observation has a positive impact on rehabilitation of motor deficits and is associated with a significant rise in activity in the bilateral ventral premotor cortex, bilateral superior temporal gyrus, the supplementary motor area, and the contralateral supramarginal gyrus in fMRI, thus including regions that are not including in the mirror hypothesis (Ertelt et al., 2007). An extensive overlap of parietal networks activated during action execution and observation support that the entire distributed neural network responsible for the execution of action rather than the concept of "mirroring" may be needed for the understanding the actions of others (Tessari et al., 2007). The improvement lasted for at least 8 weeks after the end of the intervention (Ertelt et al., 2007). Disruptive TMS (1 Hz) over the ventral premotor cortex reduced the beneficial effect suggesting that the fMRI activation in premotor cortex during action observation was functionally relevant, at least for the beneficial effect that action observation exerts over motor training (Cattaneo et al., 2011). Neurophysiological data support that action observation is accompanied by specific and differential changes in cortico-motor excitability within the hand motor representation in the primary motor cortex (Celnik et al., 2008).

Patients with parietal damage can show impairments in their ability to imitate or understand an observed action, but they may also have difficulties in monitoring early phases of their own movement planning. Both problems may occur after a parietal lesion. EEG and the readiness potential, RP, a marker of motor preparation which appears when preparing to observe an action (Kilner et al., 2004) were registered in patients with parietal lesions and in patients with a ventral premotor cortex lesion and with neurologically normal controls in an interesting recent study. All individuals were requested to watch passively a video showing an actor grasping a colored object that cued the subjects that the actor was about to move. Neurologically normal subjects and patients with a ventral premotor cortex lesion exhibited a significant RP prior to the observed action, whereas no such RP was observed in the patients with parietal lesions. The results indicate that parietal activity during action observation does not only or essentially reflect a mirroring process but rather involves an anticipatory process that may arises through prior learning and predictive mechanisms (Fontana et al., 2012).

Activation patterns in anterior regions of inferior frontal gyrus suggest dissociable operation when observing and executing actions, and caution should be exercised when claiming that activations in many locations during action observation indicate the operation of mirror neurons (Press et al., 2012).

MOTOR IMAGERY

Motor imagery accompanied by a voluntary inhibition of the actual movement activates regions that are involved in movement preparation and execution (Lotze and Cohen, 2006). Mental training has the advantage that it can start early, is easy to use and cost effective. That mental training can improve motor function and alter cortical representation areas is well documented in healthy individuals (Pascual-Leone et al., 2005; Nyberg et al., 2006; Olsson et al., 2008). Thirteen consecutively admitted patients between 4 weeks and 1 year post-stroke with stable motor deficits in their affected upper limbs received 1 h of therapy three times a week for 6 weeks. During the same period, eight patients participated in 10-min guided imagery sessions after each therapy session as well as practicing imagery at home twice each week. Therapy only remained the same but therapy + imagery group scores improved significantly (Page et al., 2001a,b). Chronic stroke patients were trained three times per week for 10 weeks and fMRI was performed before and after intervention. Post intervention fMRI showed a significant increase in activation to wrist flexion and extension of the affected hand in the premotor area and primary motor cortex on both sides, as well as in superior parietal cortex ipsilateral to the affected hand (Page et al., 2009). The positive effect remained 3 months after participation of the study (Page et al., 2011). It has recently been proposed that mental practice might also be of interest for reducing stroke-induced motor speech disorders (Page and Harnich, 2012).

Combined motor and mental training activate both the motor and the visual regions in fMRI (Nyberg et al., 2006). In addition, motor and mental training significant increased in tapping performance on an untrained sequence (transfer), and fMRI scanning indicated that the transfer effect involved the cerebellum. The conclusion was that combined motor and mental training improves motor flexibility via connections from both motor and cognitive systems to the cerebellum (Olsson et al., 2008).

In a program with home-based motor imagery training for gait rehabilitation 3 days a week for 6 weeks of patients with post-stroke hemiparesis, starting 3 months or later after stroke onset, the gains were largely maintained 3 weeks after the trial (Dunsky et al., 2008). A recent Cochrane database systemic review concludes that mental practice in combination with other treatment appears more effective in improving upper extremity function than the other treatment alone, but that further studies are needed (Barclay-Goddard et al., 2011).

VIRTUAL REALITY

Virtual reality technologies provide multimodal, interactive, and realistic 3D environments with a high level of control of the parameters and applications that can be adjusted for each user and combined with other techniques (Broeren et al., 2008; Tsirlin et al., 2009). Greater change in velocity and walking distance both in the laboratory and in the community was obtained when the robot was coupled with virtual environments in gait training (Mirelman et al., 2008). Mixing several tasks in one session produced better retention than training only one task, and in acute and sub-acute stages of recovery it would be more effective to focus rehabilitation on restoration of impairment and avoid a premature emphasis on compensation (Huang and Krakauer, 2009; Da Silva Cameirao et al., 2011). Virtual-reality games may enhance the effect of robot training on attention, speed, force, precision, and timing in the arm (Takahashi et al., 2008). A recent meta-analysis to determine the added benefit of VR technology on upper arm motor recovery concluded that VR and video game applications are potentially useful technologies that can be combined with conventional rehabilitation for upper arm improvement in motor function (Saposnik et al., 2011).

Unilateral spatial neglect is present in almost 50% of patients with right-hemisphere stroke and has a negative impact on functional recovery after stroke. A virtual reality supermarket has been used both for assessment and treatment of neglect (Ansuini et al., 2006; Broeren et al., 2007; Rand et al., 2009). Assessment of spatial attention and neglect with a virtual wheelchair navigation task has shown promise as a sensitive, efficient measure of real-life navigation (Buxbaum et al., 2008). A three-dimensional virtual street program has been developed for assessment and training extra-personal neglect and enables outdoor mobilization (Kim et al., 2010). With an fMRI-compatible VR system interfaced with robots, movement tracking, and sensing glove systems it has been shown that VR spatial brain processing differs from brain fMRI in reality and activates additional brain areas (Adamovich et al., 2009). In evaluation of possible restoration effects caused by VR training it is therefore important to integrate information about the brain activation area networks elicited by the training in VR. Combining VR and fMRI in intact brains has confirmed differences and commonalities of brain processing in VR and demonstrated the benefit of fMRI as an evaluation tool for the mental processes involved in virtual environments (Beck et al., 2010).

NEGLECT

Neglect is an important negative prognostic factor. Current concept of neglect is that it is not located to specific region but related to the attention networks. Connectivity in two largely separate attention networks located in dorsal and ventral fronto-parietal areas was assessed at acute and chronic stages of recovery in a longitudinal study of patients with spatial neglect following right hemispheric stroke. Connectivity in the ventral network, part of which was damaged, was diffusely disrupted and showed no recovery. In the structurally intact dorsal network the inter-hemispheric connectivity in posterior parietal cortex was acutely disrupted but fully recovered (Corbetta et al., 2005). A longitudinal study of patients with spatial neglect has further supported a network view in understanding neglect following right hemispheric stroke (He et al., 2007). Corbetta and Shulman (2011) have argued that neglect is better explained by the dysfunction of distributed cortical networks for the control of attention than by structural damage of specific brain regions. Ventral lesions in right parietal, temporal, and frontal cortex that cause neglect directly impair non-spatial functions partly mediated by a ventral fronto-parietal attention network. Structural damage in ventral cortex also induces physiological abnormalities of task-evoked activity and functional connectivity in a dorsal fronto-parietal network that controls spatial attention. The anatomy and right-hemisphere dominance of neglect follow from the anatomy and laterality of the ventral regions that interact with the laterality of the ventral regions that interact with the dorsal attention network. This and other studies indicate that neglect is better explained by the dysfunction of distributed cortical networks for the control of attention than by structure damage of specific brain regions (Corbetta and Shulman, 2011; Urbanski et al., 2011). Perception–attention deficits showed the most variability in the course of recovery making them prime candidates for intervention (Rengachary et al., 2011).

The aim with non-invasive stimulation for neglect is to reduce the imbalance between the two hemispheres. Most studies have so far done this by reducing the activity in the intact posterior parietal cortex with low-frequency TMS. An alternative approach is to stimulate the damaged side. Both effect of cathodal transcranial direct current stimulation (tDCS) applied over the intact posterior parietal cortex and the facilitating effect of anodal tDCS applied over the damaged posterior parietal cortex reduce symptoms of visuospatial neglect (Sparing et al., 2009). For extensive reviews on the different methods used to ameliorating spatial neglect with TMS and tDCS see Fierro et al., 2006; Cazzoli et al., 2010; Hesse et al., 2011).

Another non-invasive stimulation that may have a longer effect is continuous theta-burst stimulation (cTBS). When applied over the left posterior parietal cortex in 10 sessions over a 2-week period it accelerated recovery of hemispatial neglect. Hyperexcitability of the left parieto-frontal circuit was reduced following treatment with real but not sham cTBS, and the improvement remained 1 month after the treatment (Koch et al., 2012).

The potential role of the emotional state in modulating awareness after stroke has been tested in patients with chronic visual neglect. The visual awareness increased when tasks were performed under preferred music conditions relative to un-preferred music or silence (Soto et al., 2009). Emotional responses were associated with enhanced activity in the orbitofrontal cortex and cingulate gyrus. Improved awareness of contralateral (left) targets and a strong functional coupling between emotional areas and attention related brain regions was noted in spared areas of the parietal cortex and early visual areas in the right hemisphere. These findings suggest that positive affect, generated by preferred music, can enhance attention and decrease visual neglect, most likely due to enhancing attention.

NON-INVASIVE CORTICAL STIMULATION IN LANGUAGE

Transcranial direct current stimulation over Broca's region improves phonetic and semantic fluency in healthy individuals (Cattaneo et al., 2011). Significant improved naming accuracy has been obtained with anodal rDCS over the left frontal cortex in chronic stroke (Baker et al., 2010). Inhibiting the right Broca's homolog area by cathodal tDCS also improves picture naming in patients with chronic aphasia (Kang et al., 2011).

Sub-acute stroke patients with non-fluent aphasia were randomly divided into three groups that received either anodal tDCS applied to the left superior temporal gyrus, sham tDCS, or cathodal tDCS to the right superior temporal gyrus. All patients received conventional speech and language therapy and all patients improved. However, auditory verbal comprehension improved significantly more in patients treated with a cathode, as compared to patients in the other groups (You et al., 2011).

Low-frequency (1 Hz) rTMS applied to the homolog to Broca's area 20 min per day for 10 days have been used in a series of studies applied to the homolog to Broca's area. Sustained language improvement up to 8 months subsequent to TMS stimulation were observed in 12 non-fluent persons with aphasia 2–6 years post-stroke (Barwood et al., 2011a). In a following study, six real and six sham placebo stimulations were applied with effect only in the real stimulation groups (Barwood et al., 2011b). The electrophysiological correlates associated with the application of rTMS were studied by recording the semantic based N400 ERP measures at baseline, 1 week and 2 months subsequent to stimulation. The N400 ERP represents the capacity of rTMS to modulate neuronal language networks and measures of lexical–semantic function in participants with non-fluent aphasia. No difference was observed between baseline and 1 week but significant effect was obtained at 2 months. The authors proposed that time may be an important factor in brain reorganization subsequent to rTMS (Barwood et al., 2011c).

Melodic intonation therapy for severe non-fluent aphasia is an old method that has been systematically applied and evaluated in recent years (Norton et al., 2009). It includes three components; melodic intonation, intense training 1.5 h/day 5 days a week for several weeks, and simultaneous rhythmic tapping with the left hand (corresponding to the right unaffected hemisphere) to prime the sensorimotor and premotor cortices on the right side for articulation. It may lead to remodeling of the right arcuate fasciculus, a fiber bundle that combines the anterior and posterior language area in the left hemisphere, indicating that plasticity can be induced in the contralateral homolog tract in the unaffected hemisphere (Schlaug et al., 2009). Combining melodic intonation therapy with anodal tDCS in the posterior inferior frontal gyrus of the right-hemisphere enhanced the beneficial effect of

the training (Hamilton et al., 2011; Vines et al., 2011). For an extensive review on non-invasive brain stimulation in post-stroke aphasia, see Schlaug et al. (2011).

ACTION, GESTURES, AND LANGUAGE

Action, gestures, and language are closely related in the human brain (Rizzolatti and Arbid, 1998; Nishitani et al., 2005; Gentilucci and Corballis, 2006; Corballis, 2009). Broca's area, that traditionally was looked upon as an exclusive language area, is now considered to detect and represent complex hierarchical dependencies regardless of modalities of use including gestures, action, and music (Fadiga et al., 2009). It has been proposed to play an important role both in semantic retrieval or selection as part of a language comprehension system, and in action recognition as part of a mirror or observation–execution matching system (Skipper et al., 2007a). A network analysis of neuroimaging data has shown that interactions involving Broca's area and other cortical areas are weakest when spoken language was accompanied by meaningful speech-associated gestures, and strongest when spoken language was accompanied by self-grooming hand movement or by no hand movements (Skipper et al., 2007b). Symbolic gestures and spoken language are processed by a common neural system (Xu et al., 2009) and gestures may facilitate word retrieval in aphasia (Raymer et al., 2006). Being able to see the face and hand movements of a speaker facilitates language comprehension. Audiovisual speech perception activates network of brain regions that include cortical motor areas involved in planning and executing of speech production. When gesture accompany speech, the motor system interact with language comprehension areas to determine the meaning of the gestures, suggesting that the cortical networks underlying language comprehension are being dynamically organized by the type of contextual information available to listeners during face to face communication (Skipper et al., 2009). Co-speech gestures influence neural activity in brain regions associated with processing semantic information (Dick et al., 2009). Audiovisual comprehension activates the same fronto-temporo-parietal network of regions known for their contribution to speech production and perception. However, there are age-related differences in the functional interaction among these regions (Dick et al., 2010). Speech and co-speech gestures are usually produced together and gestures and not unambiguously understood without speech. On the contrary, pantomimes are not necessarily produced together with speech and can be easily understood without speech. Posterior STS/MTG and LIFG are differentially involved in multimodal integration, crucially depending upon the semantic relationship between the input streams. IMITATE, an intensive computer-based treatment for aphasia based on action observation and imitation, has been introduced but no results are available at this time (Lee et al., 2010).

MUSIC THERAPY

Music is a multimodal stimulus that activates many brain structures related to sensory processing, attention, and memory, and can stimulate complex cognition and multisensory integration (Zatorre et al., 2007; Koelsch, 2009; Thaut et al., 2009). The modular view of music processing with music-specific neuronal regions

and networks is challenged by the alternative view that there is a significant overlap between neuronal structures used for language and music processing. There are evidence for shared neural processing resources between the phonological/semantic aspects of language and the melodic/harmonic aspects of music (Patel, 2003, 2008; Koelsch et al., 2004; Patel and Iversen, 2007; Besson et al., 2011).

Listening to rhythm activates motor and premotor cortices (Zatorre et al., 2007; Chen et al., 2008; Bengtsson et al., 2009), and rhythmic auditory stimulation and musical motor feedback can improve gait and arm training (Schauer and Mauritz, 2003; Thaut et al., 2007). Music-supported finger and arm training that significantly improved function is accompanied by electrophysiological changes, indicating better cortical connectivity and improved activation of the motor cortex (Altenmüller et al., 2009). In a community-based stroke intervention program combining rhythmic music and a specialized rehabilitation program during 8 weeks starting 44 days post-stroke, gait velocity, symmetry, and stride length improved more than in the control groups. Stroke patients reported more positive moods and increased frequency and quality of interpersonal relationships compared to the control group (Jeong and Kim, 2007).

Daily listening to self-selected music may improve verbal memory and attention after stroke (Särkämö et al., 2008). Musical training has extensive effects on the brain. One aspect that may be relevant for stroke rehabilitation is that musicians have enhanced subcortical auditory and audiovisual processing of speech and music (Musacchia et al., 2007, 2009). Musical experience shapes brainstem encoding of linguistic pitch patterns (Wong et al., 2007), and musical training results in enhanced ability to hear speech in background noise (Parbery-Clark et al., 2009; Shahin, 2011; Strait and Kraus, 2011). Auditory attention is important for the development and maintenance of language-related skills, and musical training may aid in the prevention, habilitation, and remediation of individuals with a wide range of attention-based language, listening, and learning impairments (Strait and Kraus, 2011). The capacity to hear speech-in-noise is reduced in aging (Musacchia et al., 2009; Zamora-López et al., 2009). Significant improvements in speech-in-noise perception have been obtained in adult individuals with no prior music training with a training program that incorporated cognitively based listening exercises to improve speech-in-noise perception (Song et al., 2011). The beneficial effect was retained 6 months after the end of the study. Problem with hearing speech-in-noise is common after stroke and has considerable social consequences. It would be interesting to study if a similar program would have any effect post-stroke.

A bi-hemispheric network for vocal production is activated regardless of whether the words/phrases are intoned or spoken (Ozdemis et al., 2006), and words and melody are intertwined in perception of sung words. Some patients with aphasia are able to sing the text of a song while they are unable to speak the same text. The familiarity with the song seems to be important (Straube et al., 2008). Singing in synchrony with an auditory model (choral singing) is more effective than choral speech in improving word intelligibility (Racette et al., 2006; Gordon et al., 2010).

AGE, GENDER, AND LATERALITY

Recent developments in the quantitative analysis of complex networks, based largely on graph theory, have been rapidly translated to studies of brain network organization (Sporns et al., 2004, 2007; Bullmore and Sporns, 2009; Honey et al., 2009; Sporns, 2011). The networks span multiple spatial scales, from individual cells to cognitive systems and behavior.

Large cross-sectional study on healthy individuals ranging in age from 18 to 95 years have indicated age-related reduction in overall connectivity with age, with decreased local efficiency from the parietal and occipital to frontal and temporal neocortex in older brains. Women showed greater overall cortical connectivity and the underlying organization of their cortical networks was more efficient both locally and globally. It is proposed that it should be mandatory to take gender into account when designing experiments or interpreting results of brain connectivity/network in health and disease (Gong et al., 2009, 2011). Reduced correlations were associated with disruptions in white matter integrity and poor cognitive performance across a range of domains. Diffusion tensor imaging studies similarly indicate age-related changes in the prefrontal white matter (Malykhin et al., 2011).

The performance of the dominant arm/hand is most accurate when reaching from one fixed starting point to multiple targets, and performance with the non-dominant hand is most accurate when reaching toward a single target from multiple start locations (Sainburg and Duff, 2006; Wang and Sainburg, 2007). Studies on patients with stroke have shown differences that reflect these differences (Schaefer et al., 2007, 2009, 2011). The side of the lesion influence bilateral activation in chronic post-stroke hemiparesis (Lewis and Perreault, 2007) and the arm use after left or right hemiparesis is influenced by hand preference (Rinehart et al., 2008). The inter-hemispheric inhibition is stronger from the dominant to the non-dominant side than in the opposite direction. A similar pattern, but reduced lateralization for inter-segmental coordination is seen in lefthanders, possibly due to environmental pressure for right-handed manipulations (Przybyla et al., 2012). Modulating activity in the motor cortex affect performance for the two hands differently depending on which hand is stimulating. In two right-handed age groups, 20–40 years and 60–80 years of age, measures of final position accuracy, precision and trajectory linearity showed robust asymmetries in the left and right arms only in the young adults (Przybyla et al., 2011).

Gene expression profiles assessed in the hippocampus, superior–frontal gyrus, and postcentral gyrus of 55 cognitive intact individual aged 20–99 years demonstrated clear gender differences in brain aging (Berchtold et al., 2008). Different categories of genes were predominantly affected in males vs. females, and different regions of the forebrain exhibited substantially different gene profile changes with age. Prominent change occurred in the sixth to seventh decade across cortical regions particularly in males. Globally across all brain regions, males showed more gene changes than females.

INDIVIDUAL DIFFERENCES IN BEHAVIOR AND COGNITION

A wide range of basic and higher cognitive function, including perception, motor control, memory, and the ability to introspect, can be predicted from the local structure of gray and white matter as assessed by voxel-based morphometry or diffusion tensor imaging (Kanai and Rees, 2011). The authors propose that it would be more useful to use inter-individual differences as a source of information to link human behavior and cognition to brain anatomy rather than regard them as "noise" as is common today. Individual data may show unexpected results that can be the basis for new hypotheses that can be and tested. Age independent relationships between white matter anatomy and cognitive ability are found in healthy adult populations. Studies using diffusion-weighted magnetic resonance imaging support that inter-individual variation in white matter structure has consequences for behavior and may predict how well patients will respond to specific interventions (Johansen-Berg, 2010).

Genetic polymorphisms contribute to the increasing heterogeneity of cognitive function in old age. Brain-derived growth factor (BDNF) has a critical role in activity-dependent modulation of synaptic plasticity in human motor cortex. A common single nucleotide polymorphism (BDNF val66met) reduces secretion of BDNF, and the activity related cortical plasticity in response to motor training (Kleim et al., 2006). It is associated with greater error and poorer retention in short-term motor learning (McHughen et al., 2010) and reduces cognitive abilities in the elderly (Cheeran et al., 2008; Miyajima et al., 2008). Genetic differences may have increasingly large effect on cognition when the cognitive resources are reduced in aging. Thus the effect of the catechol-O-methyltransferase (COMT) gene heterogeneity on cognitive performance is magnified in old age and interacts with BDNF gene heterogeneity (Lindenberger et al., 2008).

Aging is associated with a progressive decline of perception, motor behavior and cognition, and memory functions (Dinse, 2005; Persson et al., 2006). However, there is considerable individual variation and high physical and cognitive activities may reduce the aging-related decline (Kramer and Erickson, 2007). An interesting study on elderly individuals with multi-year dancing
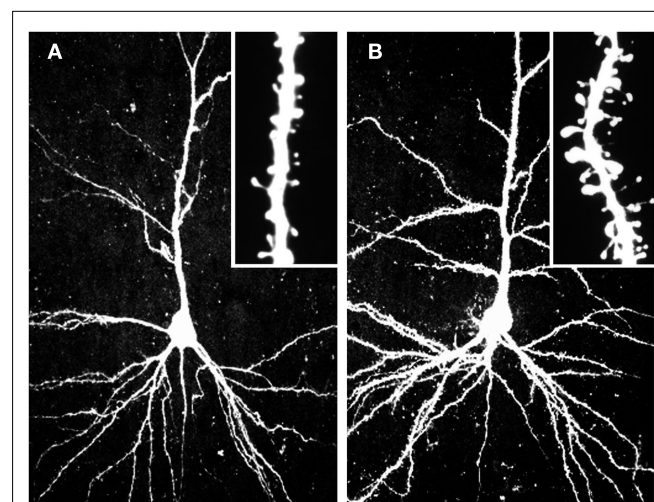

FIGURE 1 | Dendritic branching and spines in pyramidal neurons in parietal cortex in rats housed in standard laboratory cages (A) and rats in enriched environment with opportunity for various activities (B), Johansson and Belichenko (2002).

activities showed highly significant superior sensory, motor, and cognitive performance control group. Dance clearly involve multisensory stimulation and interactions that in addition to training physical activity, include motor coordination and balance, emotional stimulation, social interaction, sensorimotor stimulation, and clearly creates an enriched environment (Kattenstroth et al., 2010).

There is also substantial evidence from animal studies that a stimulating environment, before and/or after a stroke can reduced the impact of an ischemic lesion (Johansson, 2000, 2004). **Figure 1** shows the dendritic morphology of pyramidal neurons in layer II/III in rat housed in standard (**Figure 1A**) or in an enriched environment (**Figure 1B**) as viewed in confocal laser scanning microscopy after microinjection of Lucifer yellow into the neurons (Johansson and Belichenko, 2002). Post-ischemic enriched environment also improves motor and cognitive functions, stimulates neurogenesis in the subventricular zone (Komitova et al., 2005), and reduces secondary thalamic atrophy after grafting (Mattsson et al., 1997).

CONCLUDING REMARKS

Stroke unit care is the only treatment that so far has been shown to have a major impact on the outcome after stroke. More patients can return home early, and the need for institutional care is reduced (Dewey et al., 2007; Stroke Unit Trialists' Collaboration, 2007; Indredavik, 2009). The benefit of stroke units compared to general wards is most likely a combination of optimal medical and nursing care, well functional teams, task oriented, and

for the individual meaningful training in an environment that gives them confidence, stimulation, and motivation (Johansson, 2011). Cognitive rehabilitation programs starting early after stroke are essential to establish whether attention-training (Barker-Collo et al., 2009), or non-invasive cortical stimulation can lead to better social adjustment and quality of life post-stroke. Working memory and attention are important in most cognitive activities. In pilot studies, anodal tDCS over the left dorsolateral prefrontal cortex has been reported to enhance working memory (Jo et al., 2009) and to improve post-stroke attention decline (Kang et al., 2009).

Progress of time is an independent covariate that reflects spontaneous recovery of function during the first months after a stroke. To avoid the confounding effect of time (Kwakkel et al., 2006) most studies on testing new rehabilitation methods have been performed several months after stroke. Optimal benefits for the patients and the society would supposedly be obtained by successful intervention in the sub-acute phase as indicated by the beneficial effect on motor outcome in stroke units (Dewey et al., 2007; Indredavik, 2009). Rehabilitation program may require different therapy protocols in acute and chronic stages of recovery, and we need to know the optimal time for specific interventions.

The progress in research on cortical network reorganization after stroke (Wang et al., 2010; Grefkes and Fink, 2011; Westlake and Nagarajan, 2011) will increase our possibilities to test hypotheses related to treatment and outcome. One important question concerns the optimal time for starting non-invasive brain stimulation for cognitive functions. The optimal time and stimulation location may vary with the time post-stroke.

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