

Aging and Synaptic Plasticity: A Review

Jorge A. Bergado and William Almaguer

International Center for Neurological Restoration. Havana, Cuba

SUMMARY

Aging affects all systems, but the brain seems to be particularly vulnerable to the action of negative, age-dependent factors. A gradual loss of memory functions is one of the earliest and most widespread consequences of brain aging. The causes for such impairment are still unclear. Long-term potentiation (LTP) is one form of neural plasticity, which has been proposed as the cellular correlate for memory. LTP is affected by aging, and such alteration might be causally related to memory dysfunction. In the present paper, we review the evidence sustaining the existence of a causal link between cognitive and LTP impairments, as well as the possible mechanisms involved. New results indicate a possible involvement of a deficient reinforcement of LTP by affective influences.

INTRODUCTION

Aging, in biological or cosmological dimension, is the most evident consequence of the passing of time. Time is one of the coordinates (along with space) that form the referential frame in which we exist. It is difficult to assess whether time itself has any influence on living organisms. More probable are thermodynamically irreversible processes that

occur in a timely organized sequence, those responsible for aging and for giving us the sense of the passing of time. In biological terms, the aging process is accompanied by a progressive multi-systemic deterioration which, in the absence of other factors (like accidents or disease), inevitably leads to death.

Although there appears to be little hope at present of reaching immortality, major improvements in living conditions and medical care during the last century have brought a steady and significant lengthening of human life (at least for a part of mankind). Consequently, one of the main goals of modern science is to provide a better quality to those years added to life by retarding, reducing, or eliminating (when possible) the negative consequences of aging. Any progress in this direction will be based on a better understanding of the mechanisms involved in the progressive impairments accompanying aging.

The preservation of memory abilities, in both senses, namely, the ability to learn new information and to retrieve old contents, is among the most desired because it is precisely one of the more severely affected by aging. A widely accepted view at present attributes memory formation and consolidation to functional modifications at synapses in different regions of the brain. Whereas the brain system serving particular forms of memory (declarative, motor skills, emotional, classical conditioning, and others) might be different, the basic mechanism modifying synaptic efficacy seems to be common (Matthies, 1998; Medina et al., 2002; Milner et al., 1998).

Prof. Jorge A. Bergado, International Center for Neurological Restoration (CIREN) Ave. 25 # 15805 11300 Playa Ciudad de La Habana, Cuba; e-mail: bergado@neubas.sld.cu

Long-term potentiation (LTP) of synaptic efficacy (Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973) is a long-lasting increase in synaptic efficacy after high frequency (tetanic) stimulus, and appears as the best candidate mechanism for explaining the learning-induced changes in synaptic connectivity. A growing body of evidence links LTP and memory. This evidence is based, not only on the suggestive and numerous analogies between both phenomena but also on direct experiments demonstrating a relation between changes in synaptic efficacy and memory in different brain structures as well (Bergado et al., 1988; Matthies et al., 1986; Rioult-Pedotti et al., 1998; Rogan et al., 1997) (for a recent review on the subject see Martin & Morris, 2002). It is plausible, therefore, that age-related disorders in synaptic plasticity might be functionally linked to memory impairment (Shapiro, 2001). These concepts are beginning to gain consideration for the effective prevention or treatment of such impairments (Rosenzweig, 1996).

In the present review we will focus our attention on describing how LTP is affected by aging, stressing new results linking memory and emotional disorders with the modulation of LTP in aged animals.

THE GENERAL PROBLEM OF AGING

Several hypotheses have been forwarded to explain the causes of aging. General theories emphasize the role of alterations in biological membranes, the attack of free radicals, calcium dysregulation, and (particularly in mammals) the negative effect of glucocorticoids and stress (Lynch, 1998b). Obviously, all the mentioned factors strongly interact with each other and might potentiate reciprocally, obscuring the possibility to develop a testable hypothesis regarding which might be the primary events in aging.

What appears clear is that aging is a process, and that aging is caused by the action of multiple factors. Aging affects all systems: Muscles weaken, bones become fragile, skin shrinks, arteries harden, hormones (particularly sex hormones) decay, immunity fades and memory fails.

Aging and the nervous system

The alterations in nervous system function as a consequence of aging are diverse. Aged persons (and animals) move different, sleep different, and show alterations in mood and memory. Neuron death and loss of afferents have been proposed as primary events leading to brain dysfunction (Morrison & Hof, 1997; Ward et al., 1999). Although neuron death in specific brain regions is common in neurodegenerative diseases (Barili et al., 1998; Gerlach & Riederer, 1996; Graeber et al., 1998; Landfield et al., 1992; Morrison & Hof, 1997; West, 1993), the relative contribution of this factor to impairment in normal aging is a matter of debate (Rapp & Gallagher, 1996; West, 1993). Non-neuronal alterations like an impaired blood flow (Ajmani et al., 2000) or glial dysfunction (Sykova, 2001) should also contribute to a generalized brain malfunction.

Aging and memory impairment

The decline in cognitive capacities in humans is one of the earliest, most dramatic, and generalized consequences of aging. Even in normal aged persons, memory dysfunctions limit intellectual abilities. In several pathological, age-related conditions, whether vascular or neuro-degenerative like Alzheimer's disease and other dementias, the impact of age on cognition is devastating. The literature showing memory alterations as a consequence of aging in rodents (Ando & Ohashi, 1991; Kadar et al., 1990; Luparini et al., 2000; Ward et al., 1999; Ward et al., 1999), as well as in humans (Albert, 1997; Langley & Madden, 2000; Soininen

et al., 1994) and non-human primates (Bachevalier, Landis et al., 1991) is extensive. The cholinergic hypothesis of geriatric memory dysfunction (Bartus, 2000; Bartus et al., 1982) stresses the importance of the cholinergic afferents arising from the basal forebrain in memory functions (Baxter et al., 1999; Ikegami, 1994; Ikegami et al., 1992; Pedigo Jr, 1994; Russell, 1996; Shen et al., 1996; Smith et al., 1995) and has inspired some promising efforts in the search for effective treatments to overcome the age-related cognitive impairments (Fernández et al., 1994; Fischer, 1994; Fischer et al., 1994; Flood et al., 1996; Garrone et al., 1998; Levin & Torry, 1996; Scali et al., 1994; Sirvio, 1999; Smith et al., 1999; Vannucchi et al., 1997). Despite the intensive effort and literature supporting the cholinergic hypothesis, no clear picture has emerged on how acetylcholine might act to support memory processing.

When the methodological basis of animal learning models was established in the early years of the 20th Century, it was immediately recognized that for an animal to learn something a strong motivation must be present. Much less attention has been paid, however, both clinically and experimentally, to the possible impact of dysfunctional emotional-motivational reactions on cognitive performance. Such neglect might appear surprising considering that aged related alterations in mood are widespread (Blazer, 1987) and often associated with neurodegenerative diseases (Harwood et al., 2000).

AGING AND SYNAPTIC PLASTICITY

Mechanisms of plasticity

Decades of intensive research have contributed to clarify the mechanisms involved in the induction, development, and maintenance of LTP. Although different forms of LTP seem to exist—according to the induction mechanisms involved—the most common form requires the activation of

NMDA-type glutamate receptors (Bashir et al., 1991; Bashir et al., 1990; Collingridge, 1987; 1992). The NMDA ionophore allows the entrance of calcium to the postsynaptic region, an event that seems decisive to the strength and direction of the plastic modification. When the increase in Ca^{++} is above certain values, an increase in synaptic efficacy (i.e., LTP) develops, but lower values could lead to the opposite, a reduction in synaptic efficacy (the so called Long-Term Depression, LTD) (Cormier et al., 2001; Foster & Norris, 1997; Teyler et al., 1994). In LTP, Ca^{++} activates protein kinases; whereas phosphatases are activated in LTD.

Several kinases have been proved to participate in the event cascade involved in LTP; among them, the Ca^{++} -calmodulin dependent protein kinase II (PKII), the Ca^{++} -phospholipid dependent protein kinase C (PKC), and the cyclic AMP dependent protein kinase A (PKA) (Abel et al., 1997; Colley et al., 1990; Fukunaga et al., 1996; Huang & Kandel, 1994; Matthies & Reymann, 1993; Reymann et al., 1988a; 1988b; Silva et al., 1992; Stevens et al., 1994). These enzymes can modify synaptic efficacy by acting pre- and post-synaptically. For example, PKII can increase the conductance of the AMPA-glutamate receptors (Derkach et al., 1999), and consequently, increase the level of post-synaptic depolarization. But they can also act at distant regions, like the nucleus, regulating gene expression and protein synthesis (Nguyen & Kandel, 1996; 1997; Pontzer et al., 1990).

The dependency of late phases of LTP (L-LTP, >4 h) on protein synthesis is well established (Frey et al., 1988; Krug et al., 1984; Otani & Abraham, 1989). Such dependency has led to a multi-phase model of LTP, similar to that proposed for memory (Matthies et al., 1990). Yet, the identification of specific proteins required for LTP late maintenance has proven difficult. It seems that in a first step, proto-oncogenes are activated (Abraham et al., 1991; Bishop et al., 1994; Roberts et al., 1996), which can, in turn, activate structural genes; like

those coding subunits of AMPA receptors (Desmond & Weinberg, 1998).

The mechanism to guarantee LTP specificity after massive, non-specific protein synthesis requires the setting of a tag at the activated synapses, so that arriving proteins can be 'captured' only by those synapses that have been previously activated above a certain limit (Frey & Morris, 1997; 1998).

Although the incorporation of new AMPA receptors might well subserve an increased synaptic efficacy in potentiated synapses, one can't help but wonder why so many other proteins are needed. One likely explanation is that really long, long-lasting changes in synaptic efficacy are accompanied by morphological changes at the existing synapses—a possibility raised in early studies (Desmond & Levy, 1986a; 1986b; 1988; Fifkova, 1985)—or the growth and establishment of new functional synaptic contacts. Electron microscope studies reveal signs of dendritic spine division and axonal sprouting days after induction of LTP by strong stimuli (Geinisman, 1993; Geinisman et al., 1989; Yuste & Bonhoeffer, 2001).

Recent developments have shown that the plastic processes initiated by the activation of specific glutamatergic synapses can be modulated by synapses different from those previously involved in LTP induction (i.e., hetero-synaptically). This point is conceptually important because LTP has been considered a homosynaptic phenomenon, despite evidence indicating the need for hetero-synaptic cooperation. An impaired LTP has been reported in animals bearing lesions of the fimbria-fornix, the fiber system providing the hippocampus with cholinergic and aminergic fibers of sub-cortical origin (Bergado et al., 1996; Buzsáki & Gage, 1989). Cooperation between the perforant pathway (mainly glutamatergic) and the septum (mainly non-glutamatergic) and the locus coeruleus (mainly noradrenergic) has also been documented (Harley & Sara, 1992; Kitchigina et al., 1997;

Robinson & Racine, 1982; 1986).

More recently, a group of studies has shown that the activation of the amygdala—a limbic structure related to emotion (Quirk et al., 1996)—can influence the induction of LTP at the dentate gyrus (Akirav & Richter-Levin, 1999; Ikegaya et al., 1995; Ikegaya et al., 1996). We have recently shown that the electrical stimulation of the amygdala also contributes to the maintenance of LTP, converting a short lasting early-LTP (E-LTP <4h) into a late-LTP (L-LTP >4h) (Frey et al., 2001). Interestingly, the effect is protein-synthesis dependent and requires the activity of noradrenergic and cholinergic inputs. Lesioning of the fimbria-fornix, the main source of subcortical aminergic and cholinergic input to the hippocampal formation, impairs the reinforcing effect of the amygdala stimulation on L-LTP (Abe et al., 1998; Jas et al., 2000). The activity of the amygdala also seems crucial for the so-called behavioral reinforcement of LTP. According to this paradigm, E-LTP can also be converted into an L-LTP by giving the animals a behavioral stimulus with a strong motivational content (i.e. drinking after 24-h water deprivation) shortly before, or after, inducing LTP using a weak tetanus (3x15 impulses at 200 Hz) (Seidenbecher et al., 1995; 1997). We have recently obtained evidence that lesioning, or blocking the amygdala with lidocaine, abolishes the behavioral reinforcement of LTP (Almaguer et al., in press).

AGE-RELATED CHANGES OF SYNAPTIC PLASTICITY

Developmental changes

Like many other functions, synaptic plasticity presumably shows developmental changes during the early stages of postnatal life, followed by a period of relative stability in adulthood and then deteriorating slowly at older ages.

LTP is difficult to induce before postnatal day 5. At P15 a level similar to adults can be reached (Teyler et al., 1989), but outlasting in time the duration of LTP in adults under similar induction paradigms (Bronzino et al., 1994; 1995). Younger animals, on the other hand, seemed to be more prone to develop LTD (Dudek & Bear, 1993; Wasling et al., 2002).

Older animals show impaired synaptic plasticity

Although earlier reports pointed to a reduced synaptic plasticity accompanying age-dependent memory impairment (see for example (Landfield et al., 1972), a demonstration of LTP deterioration with aging came from a series of elegant studies from Barnes and McNaughton (1985) (according to the references available to us). These authors demonstrated an impressive parallelism between the slower rate of development and the faster decay of memory and LTP among aged rats, compared with young controls (Barnes, 1979; Barnes & McNaughton, 1985). This result was later confirmed by others (Bergado et al., 1997; de Toledo-Morrell & Morrell, 1991; de Toledo-Morrell et al., 1988; Diana, De Carolis et al., 1994; Geinisman, de Toledo-Morrell et al., 1995) showing that behavioral, electrophysiological, and histological alterations were more profound in old rats with memory impairments than in similarly old animals without cognitive impairments. Later studies showed that aged rats were also more prone to develop LTD or to reverse LTP (depotentialization) by low frequency stimulation (Norris et al., 1996).

The former doesn't mean that aged rats are unable to develop LTP. When adequately stimulated, aged rats can reach an increase in synaptic efficacy, similar to that of young animals (Diana et al., 1994; Moore et al., 1993)—even those showing memory impairment—but the former seem to require stronger stimulation, and the decay rate is faster. This phenomenon has been attributed to an

impaired “ability of aged rats' synapses to provide the sustained depolarization necessary to activate the LTP-induction cascade” (Rosenzweig et al., 1997).

POSSIBLE MECHANISMS OF IMPAIRMENT

Impaired induction?

Considering the importance of NMDA receptor activation for LTP induction, it seems plausible that any impairment in glutamatergic systems would have an impact on synaptic plasticity. In patients with Alzheimer's disease, neuropathology studies have shown that even in the early stages, the number of neurons in the entorhinal cortex is reduced (Braak & Braak, 1992; Palmer, 2002). The evidence from aged animals is not so clear, at least regarding the total number of cells originating the perforant pathway (Gazzaley et al., 1997; Merrill et al., 2000; 2001). In the rat, however, there are indications of a reduced glutamatergic influence on the EPSP (Barnes et al., 1997; Billard et al., 1997). This decline might be related to a reduction in glutamate receptors in the cortex and in the hippocampus—particularly of the NMDA type—that have been repeatedly reported in rats (Kito et al., 1990; Liang & Lu, 1992; Magnusson, 1998; Magnusson & Cotman, 1993; Tamaru et al., 1991; Wenk et al., 1991) and probably associated with a change in the subunit composition (Clayton & Browning, 2001; Clayton et al., 2002; Magnusson et al., 2002) and subtle subregional variations within hippocampal subfields (Wenk & Barnes, 2000). The activity-dependent redistribution of NMDA receptors is also affected among aged rats (Clayton et al., 2002). Nevertheless, the basic mechanisms of NMDA-receptor induction mechanism for LTP seemed to be preserved (Barnes et al., 1996).

Aging seems to provoke a shift from NMDA-

receptor calcium influx to Voltage Dependent Calcium Channels (VDCC) (Shankar et al., 1998), with the probable consequence that the increase in intracellular calcium will not reach the level required to activate Ca^{++} -dependent kinases, but sufficient to activate phosphatases (Foster, 1999; Foster & Norris, 1997). This situation would lead to the prediction that LTD and depotentiation are facilitated in aged rats, for which there is some experimental support (Norris et al., 1996). That blockade of VDCC attenuates this altered plasticity is in line with this hypothesis (Norris et al., 1998).

Other indications point to impaired regulation of protein kinases in aged animals. For PKII, a dysfunctional regulation of the alpha subunit has been reported in aged animals showing a decremental LTP (Davis et al., 2000), in contrast to those maintaining LTP beyond 3 h. An age-related decrease of cortical plasticity was found in mutant mice lacking the αCaMKII subunit (Kirkwood et al., 1997). Similarly, a reduced PKC activity and its substrates has been experimentally documented in aged animals (Casoli et al., 1996; Chang et al., 1997; Mons et al., 2001; Okuma et al., 2000).

Impaired maintenance?

The temporal course of LTP in aged animals, particularly its faster decay, suggests an absent protein-synthesis dependent L-LTP. Several reports show alteration in protein synthesis and expression pattern or early genes among aged rats after LTP induction (Lanahan et al., 1997; Mullany & Lynch, 1997). An impaired gene activation and protein synthesis might, in turn, affect the ability of axons and dendritic spines to divide, grow, and form new contacts that apparently are required for very long-lasting LTP. In aged rats, electron micro-scopic studies have evidenced that this capacity might be quantitatively altered (Chang et al., 1991; Geinisman et al., 1992). In line with this evidence are findings showing that the expression of cell

adhesion molecules required for axonal growth is impaired in aged rats (Ronn et al., 2000), indicating a deficient maintenance of LTP (Lynch & Voss, 1994).

Impaired heterosynaptic reinforcement?

As mentioned previously, the activation of heterosynaptic afferents (i.e. behavioral or amygdala-induced reinforcement) to a neuronal population, in which an E-LTP has been induced through a mild tetanus, can prolong the duration of the plastic process, converting it into an L-LTP that is protein-synthesis dependent. This effect suggests that the activation of such afferents is able to induce the activity of molecular cascades, which complement the insufficiently activated cascade by the previous glutamatergic tetanus. Norepinephrine and acetylcholine have been implicated in those effects (Frey et al., 2001). Both transmitters have been shown to induce a slowly developing potentiation in *in vitro* studies, which might correlate with their effects on L-LTP. Norepinephrine and acetylcholine, when applied to slices obtained from young animals, induce a slowly developing potentiation (Segal & Auerbach, 1997; Stanton & Sarvey, 1987), which might represent an L-LTP. The effect of NE is protein synthesis dependent (Stanton & Sarvey, 1985). Acetylcholine is responsible for theta rhythm in the hippocampus. The magnitude of LTP induced by tetani delivered at the positive theta peak was reduced in aged animals rats (Orr et al., 2001).

Recent results from our group provided the first evidence that such heterosynaptic reinforcing mechanisms might be deficient in aged rats, particularly among those animals showing memory deficits in a spatial task. Both behavioral- and amygdala-induced reinforcement are impaired, not only in cognitively deficient aged rats but also among aged rats showing no memory impairment in the Morris water maze (Almaguer et al., 2002;

Bergado et al., 2001). Both noradrenergic and cholinergic systems in the brain are affected by aging (Baxter et al., 1999; Chouinard et al., 1995; Friedman & Duckles, 1994; Isacson et al., 2002; Luine et al., 1990; Powers et al., 1988; Sherman & Friedman, 1990; Stemmelin et al., 2000) and both can activate kinase systems involved in regulating protein synthesis (Bevilaqua et al., 1997; Stratton et al., 1988).

We assume that the deficient reinforcement of LTP by amygdala or by behavioral stimulation is caused by a reduction in noradrenergic and/or cholinergic afferents to the dentate gyrus, the brain area in which both studies were carried out.

The results of these studies provide a rationale, at the cellular level, for a possible functional link between two of the major consequences of aging: memory impairment and affective dystonia.

Additional factors might increase the negative impact of aging on synaptic plasticity. Chronic stress has been shown to lead to a disruption in LTP (Sapolsky, 1999) by the excessive production of glucocorticoids (Bodnoff et al., 1995; McEwen, 1994), to which aged rats seemed particularly sensitive. Also, inflammatory cytokines (Lynch, 1998a) have been shown to affect LTP in an age-dependent manner.

Whereas a general agreement seems to have been reached on the relation between age-related impairments in plasticity and memory, some debate remains about which of the factors mentioned plays the major role in the degenerative process. We sustain the view that, most likely, all factors can be involved and interact cooperatively, leading to a continuously deteriorating plastic ability that causes, in turn, the decay in mnemonic capacities.

LINKS TO PATHOLOGY?

Another important aspect to consider is whether alterations in synaptic plasticity might be

also involved in memory losses in pathological forms of aging like Alzheimer's disease. New developments in animal models have provided indications that such a relation might exist.

The RNA for the amyloid precursor protein (APP), one of the key molecules in Alzheimer's pathogenesis, is upregulated after LTP induction in young rats, but not among aged rats regardless of whether they were cognitively impaired or not (Stephan et al., 2002). On the other hand, mutant mice lacking the APP gene, and in mice expressing the carboxy terminus of APP, released after proteolytic cleavage of the protein, showed an altered LTP maintenance (Nalbantoglu et al., 1997; Seabrook, Smith et al., 1999). Moreover, mice overexpressing mutant forms of human APP developed not only the typical histopathology of Alzheimer's but also an altered plasticity (Chapman et al., 1999; Larson et al., 1999) (see however (Fitzjohn et al., 2001).

AN IMPACT ON THERAPEUTICS?

The studies on the alterations of synaptic plasticity in aging have also provided some results of potential therapeutic implications.

General factors like caloric restriction (Eckles-Smith et al., 2000) or dietary supplement with antioxidants (vitamin E or lipoic acid) (Murray & Lynch, 1998; McGahon et al., 1999) reverse aged-dependent alterations in LTP, and improve glutamatergic transmission in the dentate gyrus. The use of calcium regulators like nimodipine or nifedipine has shown beneficial effects on LTP among aged rats (De Jong et al., 1992; Norris et al., 1998), and cholinergic agonists have improved declining LTP in aged rats (Fujii & Sumikawa, 2001).

Trophic factors are among the greatest hopes of restorative neurology in the last decades. Some have shown a direct effect on synaptic plasticity. Early reports suggested an action for epidermal

growth factor (EGF) and fibroblast growth factor (FGF), but not nerve growth factors (NGF), promoting LTP in normal and lesioned rats (Abe et al., 1992; Ishiyama et al., 1991; Terlau & Seifert, 1990). More recently, the results of *in vitro* and *in vivo* studies have shown that brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3), but again not NGF, are able to induce an LTP-like plastic development in the hippocampus (Chen et al., 1999; Kang & Schuman, 1995a; 1995b; 1996; Kovalchuk et al., 2002; Lu & Chow, 1999), thus re-opening the issue for a potential use of BDNF for the treatment of age-related memory impairments. Although NGF cannot by itself induce LTP, chronic treatment with NGF restores the ability of aged, memory-deficient rats to develop LTP (Bergado et al., 1997; Bergado et al., 1998), a result that correlates with behavioral studies showing an improvement in memory function after similar treatment (Fischer et al., 1994). We interpret this effect as mediated by the protective and restorative function of NGF on the basal forebrain cholinergic projection to the hippocampus and cortex. Similar results have been reported after the transplantation of septal fetal neurons to aged rats, or in rats with lesion of the septo-hippocampal projection (Bergado et al., 1997; Björklund & Stenevi, 1977; Fernández et al., 1994; Leanza et al., 1998). Although neurotrophic administration to the brain is technically difficult, an intensive search for new strategies could bring some promising results to this important field.

CONCLUSIONS

The accumulated evidence seems reasonably sufficient to postulate the existence of a functional link between the age-dependent impairment in synaptic plasticity and the deterioration of memory function. The knowledge about the mechanisms of LTP can lead not only to a better understanding of

the causality of memory decline with age but also to the development of new therapeutic strategies for treating it. Several lines of evidence also point to an impaired relation, at the cellular level, between affective and cognitive processes. Any progress in these important topics can represent a substantial contribution to reach the goal of successful aging, so that the years gained for life can also be an enjoyable period of existence.

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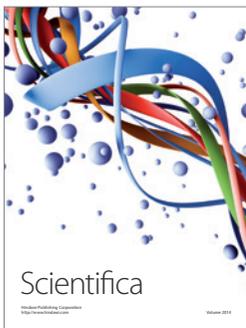
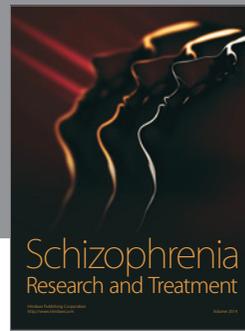
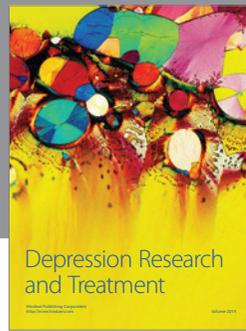
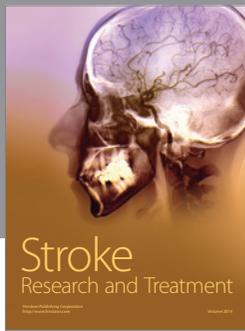
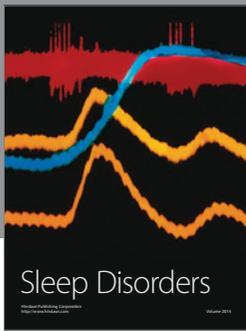
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