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Integration of the Existed Knowledge on DMN: A Critical Review Study

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Hoda Purrezaian[1]
Javad Hatami[2]

Abstract

The default-mode network (DMN) is one of the human brain's networks activated in resting and self-referential thinking states. The nature of this network and its normal or abnormal changes has been the subject of various studies. The aim of this study was to systematical review and integrating the findings of that studies focused on the relationship of DMN with mental disorders and aging-induced changes in it. Of the more than ۱۰۰ evidences found, ۳۲ studies in each of two specific subjects (psychopathological and aging-related changes of DMN) were selected and scientifically mentioned the most important results of them. Based on the findings, some of the mental disorders including major depression, generalized anxiety disorder, obsessive compulsive disorder, schizophrenia, attention-deficit hyperactivity disorder, and Alzheimer disease are associated with functional or connectional abnormalities in DMN. Aging can cause functional changes in the activation or deactivation of the DMN's regions or inter/intra-network connectivity of this network. Although most of studies have a pathological perspective on DMN changes; one article pointed out the positive role of DMN changes during aging in terms of emotion regulation.

Keywords: Default Mode Network (DMN), DMN's subsystems, Functions of DMN's subsystems, Psychopathological changes in DMN, Aging-related alterations of DMN

1. *Ph.D. Candidate in Health Psychology, University of Tehran, Tehran, Iran, e-mail: h.p209@yahoo.com
2. Associate Professor, University of Tehran, Tehran, Iran.

Introduction

The default-mode network (DMN) is a set of specific brain's regions whose activity, predominant in the resting-state (Greicius et al., 2008). The default network is engaged when individuals are left to think about themselves or other kinds of situations like freethinking, remembering the past or future events, and considering the thoughts and perspectives of other people (Buckner, Andrews-Hanna, & Schacter, 2008). This network is also active during directed tasks that require participants to remember past events or imagine upcoming events (Buckner, 2013).

However, a lot of research in other countries so far has been done to discover the default-mode network in the brain and its operation, the number of Iranian studies in this area is very few. This may be due to lack of scientific endeavors to introduce this network. Therefore, the main purpose of this paper is to announce the default network and its relationship with psychological disorders. So this paper is divided into two parts: the first one seeks to attempts to review the literature on DMN with a psychological view, and the second part will address this main question: whether the default mode network has undergone any change with aging as other brain networks or no.

Brief History

Discovery of the brain's default network was completely accidental. Box 1 shows a brief history of DMN's discovery according to Buckner et al. (2008).

Box 1
A brief history of DMN's discovery

1890	A clue that brain activity persists during undirected mentation emerged from early studies of cerebral metabolism. It was already known by the late 19^{th} century that mental activity modulated local blood flow (James, 1890).
1931	Hans Berger established that the brain is not idle when left undirected. Rather, brain activity persists in the absence of external task direction.
1955	Louis Sokoloff et al used the Kety-Schmidt nitrous oxide technique to ask whether

	cerebral metabolism changes globally when one goes from a quiet rest state to performing a challenging arithmetic problem-a task that demands focused cognitive effort. To their surprise, metabolism remained constant.
1974	David Ingvar, was the first to aggregate imaging findings from rest task states and note the importance of consistent, regionally specific activity patterns. Using the xenon 133 inhalation technique to measure regional cerebral blood flow (rCBF), Ingvar and his colleagues observed that frontal activity reached high levels during rest states. Two lasting insights emerged from Ingvar's work: a) Echoing ideas of Hans Berger, and b) Ingvar's observations suggested that increased activity during rest is localized to specific brain regions that prominently include prefrontal cortex.
1987	PET had finer resolution and sensitivity to deep-brain structures than earlier methods and, owing to the development of isotopes with short half-lives, typical PET studies included various task and control conditions for comparison.
1995	A particularly informative early study was conducted while exploring brain regions supporting episodic memory. Confronted with the difficult issue of defining a baseline state for an autobiographical memory task, Andreasen et al (1995) explored the possibility that spontaneous cognition makes an important contribution to rest states.
2001	The definitive recent event in the explication of the default network came with a series of publications by Raichle, Gusnard et al (2001). Their papers directly considered the empirical and theoretical implications of defining baseline states and what the specific pattern of activity in the default network might represent. ▪ First, they distinguished between various forms of task-induced deactivation and separated deactivations defining the default network from other forms of deactivation (including attenuation of activity in unattended sensory areas). ▪ Second, they compiled a considerable array of findings that drew attention to the specific anatomic regions linked to the default network and what their presence might suggest about its function. ▪ A key insight was that the medial prefrontal regions consistently identified as part of the default network are associated with self-referential processing. ▪ Most importantly, the papers brought to the forefront of ▪ the exploration of the default network as its own area of study (including providing its name "default network", which, as of late 2007, has appeared as a keyword in 237 articles.

Structure of DMN

The default mode network similar to any other networks of brain is connected to certain areas of the brain's lobes. The core regions associated with DMN are:

- Ventral medial prefrontal cortex (vMPFC)
- Anterior and Posterior cingulate/ retrosplenial cortex (ACC/PCC/Rsp)

- Inferior parietal lobule/ precuneus (IPL/PCU)
- Lateral temporal cortex (LTC)
- Dorsal medial prefrontal cortex (dMPFC)
- Hippocampal formation (HF) (Buckner et al. 2008; Devey, Pujol, & Harrison, 2016; Koshino, Minamoto, Yaoi, Osaka, & Osaka, 2014).

Based on the states of Andrews-Hanna (2012), these regions are divided into two subsystems and two hubs with their own functions (see figs 1 & 2).

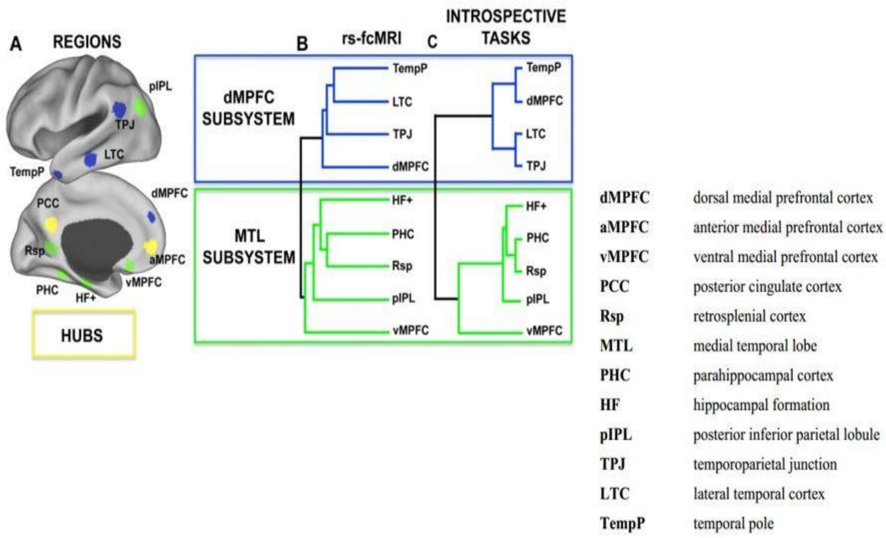

Fig 1. The DMN’s subsystems and hubs retrieved from Andrews-Hanna (2012)

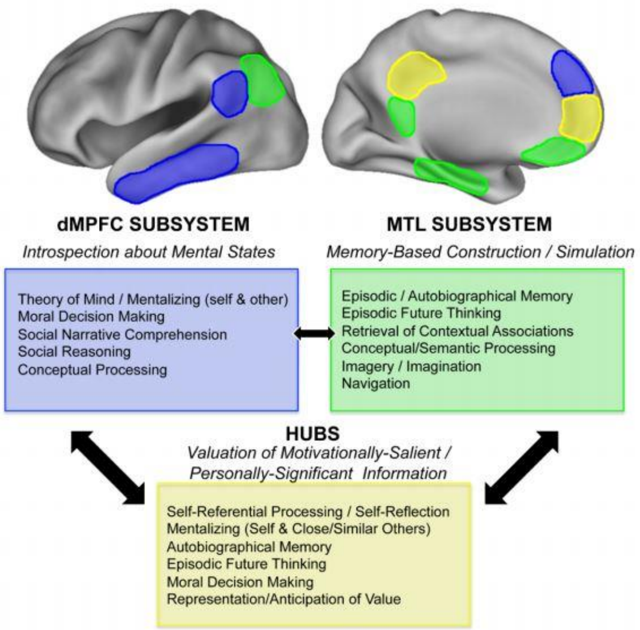

Fig 2. The functions of DMN's subsystems and hubs retrieved from Andrews-Hanna (2012)

Results

Psychopathological prospect to DMN changes

Related to the DMN's regions (subsystems and hubs) the findings of neuroimaging researches show that disruption in any parts of DMN is associated with some psychiatric and neurological diseases, including: major depression (MD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), social phobia, posttraumatic stress disorder (PTSD), schizophrenia, attention-deficit/hyperactivity disorder (ADHD), autism, Alzheimer disease (AD), stroke, chronic pain, progressive multiple sclerosis, and so on (Anticevic, 2012; Broyd et al., 2009). Table 1, shows the particular DMN disruptions for the most important psychological disorders.

Nevertheless, DMN can be changed with interventions. Effective psychological or neurological interventions on DMN's abnormalities are Meditation (Fingelkurts, Fingelkurts, & Kallio-Tamminen, 2016; Jang et al., 2010; Xu et al., 2014), Mindfulness-based therapies (Doll, Hölzel, Boucard, Wohlschläger, & Sorg, 2015; Prakash, De Leon, Klatt, Malarkey, & Patterson, 2013), Transcranial Magnetic

Stimulation (TMS) (Liston et al., 2014; Vidal-Piñeiro et al., 2015), Electroconvulsive Therapy (ECT) (Mulders et al., 2016), and some psychiatric drugs (such as Antidepressants) (Posner. et al, 2013).

Table 1. DMN disruptions in the psychological disorders

Psychological Disorder	DMN Disruption(s)	Major syndrome related symptom(s)	Research evidence(s)
Depression	- Increased functional connectivity between the DMN and subgenual prefrontal cortex (sgPFC); - Increasing levels of DMN dominance relative to the task-positive network (TPN); - Increased the DMN activity in the anterior DMN including ACC and mPFC, posterior regions including the PCC and the precuneus, and ventrally in the hippocampal formation and para-hippocampus; - More neural functional connectivity between the PCC and the subgenual-cingulate cortex during rest states, but not during task engagement; - Lower DMN connectivity in frontal, temporal, and parietal cortexes.	- Ruminatio n; - Negative self-referential; - Destructive estimates the past combined with guilty feelings; - Despair of the future; - Negative emotions.	- Berman et al. (2011) - Dai, Yin, Huang, Li, Wang, & Feng (2018) - Hamilton, Farmer, Fogelman, & Gotlib (2015) - Hamilton, Furmer, Chang, Thomason, Dennis & Gotlib (2011) - Sambatar o, Wolf, Giusti, Vasic, & Wolf (2013)
Generalized Anxiety Disorder	- Increased connectivity of left insular cortex to the DMN; - Less deactivation of the MPFC, and Greater deactivation in PCC; - Anticorrelated rsFC of amygdala and DMN.	- Concerned about the future; - Difficulty concentrating; - Being easily fatigued Especially mentally; - Impaired emotion regulation (ER).	- Dennis, Gotlib, Thompson, & Thomason (2011) - Rabany et al. (2017) - Zhao et al. (2007)
	- Significantly	- Self-	- Apergis-

Psychological Disorder	DMN Disruption(s)	Major syndrome related symptom(s)	Research evidence(s)
OCD	reduced connectivity within the dMPFC self-subsystem; - Higher connectivity between components of the dMPFC self-subsystem and the anterior insula and the superior parietal lobe; - Impaired functional connectivity of right mPFC-left superior frontal gyrus (SFG) within DMN; - Decreased activation in several frontal regions and the posterior cingulate (PCC, BA31) together with a stronger connectivity between the PCC and the vmPFC (BA10); - Hyperconnectivity of the ventromedial prefrontal cortex; - Reduced inverse connectivity between the anterior medial prefrontal cortex (amPFC) and the anterior insular cortex; - Difficulties with the deactivation of DMN even when the non-rest condition.	Dissatisfaction; - Repetitive annoying thoughts; - Feeling guilty and restless for repetitive actions, especially during rest; - Sustained attention deficits.	Schoute, Bijleveld, Gillan, Fineberg, Sahakian, & Robbins (2018) - Beucke et al. (2014) - Fan et al. (2018) - Gonçalves et al. (2017) - Koch et al. (2018) - Posner et al. (2017)

Psychological Disorder	DMN Disruption(s)	Major syndrome related symptom(s)	Research evidence(s)
Schizophrenia	- Greater connectivity in the DMN and task-positive network; - Increased deactivation of specific DMN regions including MFG and precuneus; - Reduced deactivation of ACC; - Increased activity in the PCC altered FC of left mPFC-bilateral anterior cingulate cortex (ACC) which indicated interaction between DMN and salience network; - interaction between left mPFC and right parietal lobe; - Functional connectivity between DMN and frontal-parietal network.	- Feeling compelled to do some weird actions; - Imagination with illusion; - Apathy; - Sustained attention deficits.	- Broyd et al. (2009) - Fan et al. (2018) - Kim et al. (2014)
ADHD	- Altered patterns of functional connectivity within the DMN; - DMN exhibited more variable activation patterns; - Functional connectivity between and within attention and DMN networks.	- Difficulty concentrating; - Feeling forced to do purposeless actions even at rest; - Reduced task-performance.	- Kucyi, Hove, Biederman, Van Dijk, & Valera (2015) - Mowinckel et al. (2017)

DMN and Aging

As the aging population is increasing all around the world (Moatamedy, Soltani, & Hamedi, 2019; Naeimi, Kazemi, & Dehghan, 2016) the number of scientific researches aimed at studying aging and bio-psycho-social changes in this age is also increasing. Relatively numerous studies have examined the DMN’s changes throughout the life and compared functions of this network in the elderly and young people (Ng, Beason-Held, Kraut, & Resnick, 2009; Damoiseaux et al., 2008; Damoiseaux, Prater, Miller, & Greicius, 2012; Greicius, Srivastava, Reiss, & Menon, 2004; Hafkemeijer, Grond, & Rombouts, 2012; Koch et al., 2010; Lo, Lim, Chee, & Zhou, 2016; Mevel, Chetelat, Eustache, & Desgranges, 2011; Onoda, Ishihara, & Yamaguchi, 2012; Ouchi, & Kikuchi, 2012; Prakash, Heo, Voss, Patterson, & Kramer, 2012; Sala-Llonch, Bartrés-Faz, & Junqué, 2015; Salami, Pudas, & Nyberg, 2014; Sambataro et al., 2010; Vidal-Piñeiro et al., 2014; Wang et al., 2015; Wang et al., 2014; Wang et al., 2013; Zhang et al., 2014). Since these studies have reported almost similar or parallel findings, we will review some of them as exemplary.

A meta-analysis study has compared the brain changes during normal aging and Alzheimer disease. The findings of this meta-analysis show that in healthy elderly, a decreased functional connectivity was demonstrated in a variety of DMN brain regions. These included the PCC, superior and middle frontal gyrus, and the superior parietal region. While in these studies younger and older subjects were compared, one multicenter study analyzed subjects with a continuous age range from 18 to 71 years, showing a negative association between age and DMN connectivity. Task-induced deactivation in healthy aging has been reported in two studies showing decreased DMN deactivation in the elderly. Elderly subjects showed a decreased task-induced deactivation in the PCC and medial parietal regions compared to younger adults. Furthermore, a gradual, age-related decreased deactivation in the DMN was observed when comparing younger, middle-aged, and older adults. These results suggest that there is an age-related reduction in the ability to suspend default mode activity. While in AD patients with relatively mild memory complaints, the hippocampus already showed decreased functional connectivity with the mPFC, PCC, precuneus, and ventral ACC. When the PCC is used as seed region in this group, decreased connectivity was found with the mPFC, precuneus and parietal cortex. In addition, independent component analysis (ICA) demonstrated decreased DMN functional connectivity in patients with mild AD. Another study using ICA to analyze fMRI data during a low cognitive demand task, observed decreased resting state activity in the PCC and hippocampus, suggesting disrupted connectivity between these two regions. DMN task-induced deactivation studies in AD showed a decrease in deactivation. Decreased deactivation in medial and lateral parietal regions was observed during an associative memory paradigm in AD patients. In medial parietal regions and the PCC, decreased deactivation was observed with a semantic classification task in AD patients. The mPFC, PCC, precuneus, parietal cortex and hippocampus demonstrated decreased deactivation during a nonspatial working memory task and a visual encoding task for episodic memory in AD patients (Hafkemeijer, et al., 2012).

The results of another research show decreased activity in the older versus younger subjects in DMN, containing the superior and middle frontal gyrus, posterior cingulate, middle temporal gyrus, and the superior parietal region. These results remain significant after correction for RSN-specific gray matter volume. The relevance of these findings is illustrated by the correlation between reduced activity in one of these RSNs and less effective executive functioning/processing speed in the older group (Damoiseaux et al., 2008).

One study has examined Default Mode Network connectivity correlates with age-associated structural and cognitive changes and reported that DMN connectivity reduced with aging, specifically between mPFC and PCU areas in which connectivity was clearly lower in the old subjects group. Also, mPFC-PCU link was able to predict cognitive performance as it was significantly associated with memory factor, and with speed processing domain. The working memory and the inhibitory factor were unrelated to connectivity. Years of education was associated with all cognitive factors while age was only significantly associated with the speed processing factor; this was expected, given the small standard deviation in this variable (Vidal-Piñeiro et al., 2014).

The results of an additional related study state the old subjects in comparison to their young counterparts showed significant reductions in connections from Right inferior temporal cortex (ITC) to medial prefrontal cortex (mPFC), Right hippocampus (HP) to right ITC, and mPFC to posterior cingulate cortex; and increases in connections from left HP to mPFC and right inferior parietal cortex to right ITC (Wang et al., 2014).

Martins and Mather (2016), comparing to other researchers, have a holistic and different view to DMN changes in elderly people. In the introduction of their study (published as a book chapter) state that; however, aging is marked by cognitive declines across modalities, overall emotional experience tends to be less negative for older than younger adults. Self-reported well-being is lowest in midlife and increases after age 50, and older adults report less negative affect in daily life than younger people. Generally, older people relative to the younger show improvements in well-being, and also in outcomes linked to the regulation of emotions. Mood disorders indicating emotional dysregulation, such as depression and anxiety decrease in prevalence with age. Subclinical mood symptoms, such as ruminative thinking, also tend to decrease across the lifespan. Thus, healthy older adults appear to manage their emotional well-being better than younger adults. A possible mechanism for this shift in wellbeing may involve changes in emotion regulation brain networks. During attention-demanding cognitive tasks, DMN activity decreases and activity in the Salience Network increases. However, DMN activity decreases less as cognitive task difficulty increases among older adults. The findings of this study, indicates these age differences in DMN activity carry over to emotion regulation as follow:

- Functional connectivity decreases within the DMN for older adults; in particular, connectivity between anterior and posterior DMN regions is weaker among older than younger adults both during resting state and during cognitive task performance. The older adults also demonstrate weaker functional connectivity within the DMN during performance of a self-reflective processing task;
- Connectivity between DMN and other networks increased in later life; DMN connectivity with salience and executive networks increases. Resting state connectivity of the DMN, salience, executive, visual, and somatomotor networks, and other networks reveal less segregation with increasing age. This indicates that younger adults show greater differentiation between networks, and that age leads to greater cohesion between networks;

- Depressed individuals show greater DMN intra-network connectivity, and decreased inter-network connectivity between the DMN and other networks;
- Intra-network and inter-network default mode connectivity is enhanced for mindfulness practitioners.

So, older people may use enhanced DMN-executive network and DMN-salience network connections to increase awareness of the associations between positive interpretations and the self (and to dissociate negative interpretations from the self).

Such findings could change our views of aging, despite the cognitive decline that occurs during this retro of life.

Discussion and Conclusion

Here, in addition to examination the nature of default mode network, we reviewed the DMN's alterations and abnormalities associated with psychological disorders and aging.

According to the related researches, some of them are presented in the first part of this paper, several psychological and mental disorders are associated to functional or connectional abnormalities in DMN, in which five most important ones are mentioned in the present paper. As shown in Table 1, five of the most important psychological disorders include major depression, generalized anxiety disorder, obsessive compulsive disorder, schizophrenia, and attention-deficit/hyperactivity disorder are directly linked to disturbances in the default mode network itself or its connections to other brain networks. For example increased functional connectivity between the DMN and subgenual prefrontal cortex; increasing levels of DMN dominance relative to the task-positive network; increased the DMN activity in the anterior DMN including ACC and mPFC, posterior regions including the PCC and the precuneus, and ventrally in the hippocampal formation and para-hippocampus; more neural functional connectivity between the PCC and the subgenual-cingulate cortex during rest states, but not during task engagement; and lower DMN connectivity in frontal, temporal, and parietal cortexes, precisely leading to signs that indicate depression including rumination, negative self-referential, destructive estimates the past combined with guilty feelings, despair of the future, and negative emotions (Berman et al. 2011; Dai et al.,2018; Hamilton et al., 2015, 2011; Sambataro et al., 2013).

In addition, some of the most important symptoms of general anxiety disorder, such as concern about the future, difficulty concentrating, being easily fatigued, and impaired emotion regulation be associated to disruptions such as increased connectivity of left insular cortex to the DMN, less deactivation of the MPFC, greater deactivation in PCC, and anti-correlated rsFC of amygdala and DMN (Dennis et al., 2011; Rabany et al., 2017; Zhao et al., 2007).

The obsessive compulsive disorder also has certain indications such as self- dissatisfaction, repetitive annoying thoughts, feeling guilty, restless for repetitive actions especially during rest, and sustained attention deficits, that they can be identified with structural, functional, and communication distortions of the default mode network, like significantly reduced connectivity within the dMPFC self-subsystem; higher connectivity between components of the dMPFC self-subsystem and the anterior insula and the superior parietal lobe; impaired FC of right mPFC-left superior frontal gyrus within DMN; decreased activation in several frontal regions and the posterior cingulate together with a stronger connectivity between the PCC and the vmPFC; hyper connectivity of the ventromedial prefrontal cortex; reduced inverse connectivity between the anterior medial prefrontal cortex and the anterior insular cortex; and difficulties with the deactivation of DMN even when the non-rest condition (Apergis-Schoute et al., 2018 Beucke et al., 2014; Fan et al., 2018; Gonçalves et al., 2017; Koch et al., 2018; Posner et al., 2017).

Further, it is very easy to justify why the most famous symptoms of schizophrenia, such as feeling compelled to do some weird actions, imagination with illusion, apathy, and sustained attention deficits have direct connection with some DMN disturbances such as greater connectivity in the DMN and task-positive network; increased deactivation of specific DMN regions including MFG and precuneus; reduced deactivation of ACC; increased activity in the PCC; altered FC of left mPFC-bilateral anterior cingulate cortex which indicated interaction between DMN and salience network; interaction between left mPFC and right parietal lobe; and functional connectivity between

DMN and frontal-parietal network (Fan et al., 2018; Kim et al., 2014; Broyd et al., 2009).

After all, what can be said about the ADHD is that the most important symptoms of this disorder, such as difficulty concentrating, feeling forced to do purposeless actions even at rest, and reduced task-performance, can be explained by the presence of disturbances in the default network, such as altered patterns of functional connectivity within the default mode network; DMN exhibited more variable activation patterns; and functional connectivity between and within attention and DMN networks (Kucyi, Hove et al., 2015; Mowinckel et al, 2017).

Based on the research evidences, any disruption of the brain sectors can lead to disturbances in their unique functions. Usually these research evidences have been obtained by activating different parts of the brain and then observing functional changes. Studies on the DMN show us that the different parts of the brain maintain their functional management, even in the rest situation or at deactivation mode too. In addition, proving the connection of just a network in a brain with various mental and psychological disorders is of great importance in psychology and, consequently, psychotherapy.

Second part of the current paper stated that aging can cause functional changes in the activation or deactivation of the DMN's regions or inter/intra-network connectivity of this network. Although most of studies have a pathological perspective on DMN changes (Beason-Held et al., 2009; Damoiseaux et al., 2008; Damoiseaux et al., 2012; Greicius et al, 2004; Hafkemeijer et al., 2012; Koch et al., 2010; Mevel et al., 2011; Ng et al., 2016; Onoda et al., 2012; Ouchi, & Kikuchi, 2012; Prakash, Heo et al., 2012; Sala-Llonch et al., 2015; Salami et al., 2014; Sambataro et al., 2010; Vidal-Piñeiro et al., 2014; Wang et al., 2013; Wang et al., 2014; Wang et al., 2015; Zhang et al., 2014), one study pointed out the positive role of DMN changes during aging in terms of emotion regulation (Martins, & Mather, 2016). This research gives this important message to us that all disruptions and changes caused by disease or aging in the brain are not merely destructive, but can lead to useful changes in the person's personality and lifestyle. In addition, it can be seen that the intellectual and creative blend of variables in scientific research can lead to surprising and key results.

In addition to integration the existed knowledge about the default mode network, the present study had another achievement too: discovering some research deficiencies on DMN that can be valuable for future studies. For example, there is almost not any research on the long-term effects of psychotherapy on DMN structures and functions. While it seems some of the popular psychotherapeutic systems can create such effects at least. Scientific assumption of the present researcher is that art therapy can be very effective in this area. Finally, it is therefore suggested to be investigated this idea by future researchers and therapists, and taking a longitudinal study up on childhood to old age about changes in different brain networks especially in DMN according to the various factors and features, too.

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