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Impairment of the executive attention network in premenopausal women with hormone receptor-positive breast cancer treated with tamoxifen

Xingui Chen[a,b], Jingjing Li[c], Jingjie Zhang[d], Xiaoxuan He[e], Chunyan Zhu[b], Lei Zhang[b], Xinglong Hu[f], Kai Wang[a,b,*]

[a] Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, China
[b] Department of Medical Psychology, Anhui Medical University, Hefei, China
[c] Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China
[d] Department of Breast and Thyroid Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China
[e] Center for Biomedical Engineering, University of Science and Technology of China, Hefei, China
[f] Anhui Mental Health Center, Hefei, China

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ABSTRACT

Tamoxifen (TAM) is most commonly prescribed for patients with hormone-sensitive breast cancer and exerts agonistic/antagonistic effects on estrogen receptors throughout the body. Accumulating evidence has revealed that breast cancer patients receiving TAM manifest cognitive dysfunction. However, whether these patients have a global attention deficit or a more selective impairment of specific attention networks remains unknown. In the present study, we sought to explore the attention function of premenopausal women with hormone receptor-positive breast cancer treated with TAM using the attention network test (ANT). The subjects included breast cancer patients receiving TAM (TAM, N = 43), breast cancer patients not receiving TAM (non-TAM, N = 41), and matched healthy controls (HC, N = 46). The subjects completed the ANT and neuropsychological tests, which measure three independent attention networks and executive function performance, respectively. Our results indicated that patients in the TAM group had significant deficits in their executive control component but not in the alerting or orienting components. Moreover, the patients showed poor executive function performance in the neuropsychological tests. Additionally, in the TAM group, significant correlations were found between the decreased efficiency of the executive control component and their reduced performance in executive function tests. This study demonstrates that premenopausal women with hormone receptor-positive breast cancer treated with TAM have impairment of the executive attention network and that this impairment was associated with differences in executive function performance.

1. Introduction

Among the selective estrogen receptor modulators (SERMs), which are a type of endocrine therapeutic, tamoxifen (TAM) is the most commonly prescribed for patients with hormone receptor-positive breast cancer. This positive hormone receptor includes the presence of estrogen receptor (ER) and/or progesterone receptor (PR). TAM exerts differential effects on estrogen receptors throughout the body. Due to its anti-estrogen effects in the breast, TAM is effective for both the treatment and prevention of breast cancer. It also acts as an estrogen agonist, significantly increasing the incidence of hot flashes and risk for endometrial cancer, cardiovascular disease and venous thrombosis (Perez, 2007).

Cognitive impairment related to breast cancer and its treatment has become an important area of study. Accumulating evidence has shown that a subgroup of breast cancer patients receiving adjuvant endocrine therapies manifests cognitive dysfunction (Buwalda and Schagen, 2013) and that the cognitive dysfunction is an important factor that affects a patient's long-term quality of life. We recently reported that patients with breast cancer who are receiving TAM had impairments in decision-making function (Chen et al., 2014), which is considered one of the most important components in executive function. Some studies have also reported that TAM detrimentally affects verbal memory (Schilder et al., 2009; Shilling et al., 2003), visuospatial ability (Ahles et al., 2010), and processing

* Corresponding author at: Laboratory of Neuropsychology, Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei 230032, China.
E-mail address: wangkai1964@126.com (K. Wang).

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speed (Palmer et al., 2008; Schilder et al., 2010; Shilling et al., 2003). Although these studies have raised concerns about TAM treatment and cognitive deficits in breast cancer survivors, the mechanism(s) underlying these changes are still unclear.

As a major component of the cognitive function system, attention is the behavioral and cognitive process of focusing brain or mental activities. Attention has also been referred to as the allocation of limited psychological resources (Anderson, 2004). Two recent studies have shown an increase in perceived cognitive decline in patients receiving TAM, particularly in increased attention and concentration complaints, but an objective analysis of cognitive performance failed to show a significant effect (Breckenridge et al., 2012; Schilder et al., 2012). These inconsistent results may be attributed to different experimental test tools and designs. Therefore, we hypothesized that selecting a subtle assessment of attention is essential for better investigating slight or moderate changes in attention function.

Posner and Petersen (1990) proposed the Attention Network Theory, which consists of three distinct attention components. These components carry out alerting, orienting and executive functions. The alerting component is defined as the ability to maintain the alert state of a warning signal, and the alerting system is associated with the right hemisphere and the parietal cortices, which are regions that are activated by continuous alert signals (Fan et al., 2005b). The orienting component is the process of selecting information from numerous sensory inputs. Research suggests that the temporal-parietal junction and superior parietal lobe are involved in orienting the system of attention (Andersen et al., 1997). The executive control component is characterized by the resolution of conflicting information. The midline frontal areas and the prefrontal cortex are activated during conflict tasks, processing between central targets and surrounding flankers (Botvinick et al., 2001; Fan et al., 2005b). The Attention Network Test (ANT) developed by Fan et al. (Fan et al., 2002) measures these three attention components using the flanker task. The flanker task is a set of response inhibition tasks used to assess the ability to suppress responses that are inappropriate in a particular context. The ANT has been widely used to study attention function in various neuropsychological and neuroimaging studies (Markett et al., 2013) and in various types of neurological impairment, including Parkinson's disease (Zhou et al., 2012), injuries to disparate brain regions (Rinne et al., 2013), and psychiatric disorders (Hahn et al., 2011).

To our knowledge, studies regarding the cognitive deficits in the attention networks of premenopausal women with hormone receptor-positive breast cancer treated with TAM have not yet been reported. Therefore, the current study aimed to investigate changes in any of the attention networks in breast cancer patients receiving TAM treatment. On the basis of previous studies and our findings described above, we hypothesized that the patients would have executive control component deficits of the attention network. Additionally, to evaluate multiple aspects of executive function, several neuropsychological tests, including the Stroop test, the Trail Making Test (TMT), and the Wisconsin Card Sorting Test (WCST), were used. As such, we investigated whether patients receiving TAM treatment exhibited executive dysfunction and examined the relationships between and among these deficits and variations in the patients' demographic characteristics.

2. Materials and methods

2.1. Subjects

The current study was conducted in agreement with the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Anhui Medical University, in Hefei, China. The patients, who were recruited from the First Affiliated Hospital of Anhui Medical University, could speak Chinese. Breast cancer patients were assigned to the TAM and non-TAM groups, based on the presence of ER and/or PR. The TAM group included 43 breast cancer patients whose cancer tissue was positive for the ER and/or PR. In the TAM group, there were 29 patients with breast cancer diagnosis of stage I, nine patients with diagnosis of stage II, and five patients with diagnosis of stage III. Of these patients, 19 received loco-regional radiation therapy. These patients were treated with TAM (20 mg daily) for a mean of 44.9 ± 9.9 months, and TAM was administered for at least 12 months. The non-TAM group consisted of 41 breast cancer patients whose cancer tissue was negative for ER and PR. In the non-TAM group, there were 31 patients with breast cancer diagnosis of stage I, seven patients with diagnosis of stage II, and three patients with diagnosis of stage III. Of these patients, 15 patients received loco-regional radiation therapy. The duration of disease in the non-TAM group was 41.8 ± 9.3 months. In the present study, 10 patients in the TAM group and 13 patients in the non-TAM group were previously included in our first study on decision-making function. These 23 patients were subjected to the attention and executive function tests at a mean follow-up interval of 11 months after the first study. However, the data from these tests were not collected in the aforementioned study. The data from the other 61 patients were collected for the first time. Self-reporting screening questionnaires were used to screen for eligibility for participation in this study. The subjects met the following inclusion criteria: were premenopausal; no diagnosis of dementia, brain injury, or psychological disorders; no alcohol or drug abuse; and no chemotherapy treatment. The patients were free of subtle or severe affective disorders (Hamilton Depression Rating Scale scores < 8 and/or Hamilton Anxiety Rating Scale scores < 8). Additionally, 46 age- and education-matched healthy controls, who were recruited from the local university, as well as the patients' relatives also participated in this study. Following an explanation of the study objective, the subjects provided written informed consent. Detailed information on the subjects is shown in Table 1.

2.2. Neuropsychological tests

The subjects were evaluated using standardized neuropsychological tests created to investigate their fatigue symptoms, general cognitive function, and executive function. The Chinese version of the Cancer Related Fatigue test was used to exclude fatigue symptoms as a contributor to the results (So et al., 2003; CRF). The Montreal Cognitive Assessment test was administered to assess general cognitive function (Nasreddine, 2006; MoCA). The Verbal Fluency test, which was assessed general frontal executive function, required the subjects to word a specific semantic category (e.g., animals or fruits) within one minute (Chiu et al., 1997).

The Stroop test (Stroop, 1935) requires subjects to name the ink color of words meaning a different color. This test is divided into three tasks. First, the Stroop Color test requires the subjects to name the colors of dot stimuli. Second, the Stroop Word test asks the subjects to name the ink colors of non-color word stimuli (e.g., to name the red ink color of the word "walk"). Third, the Stroop Interference test requires the subjects to name the colors of color word stimuli (e.g., to name the yellow color of the word "red"). The subjects are asked to name the ink color as quickly and accurately as possible.

The Trail Making Test (Spreen and Strauss, 1998) is given in two parts, Test A (TMTA) and Test B (TMTB). For Test A, the subjects were asked to connect consecutively numbered circles in ascending order on a piece of paper, as accurately and quickly as possible. For Test B, the subjects were asked to connect the same number of consecutively numbered and lettered circles alternately (e.g., 1, A, 2, B, 3, C, etc.). The subjects were required to restart the process of