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Brain resting state functional magnetic resonance imaging in patients with takotsubo cardiomyopathy an inseparable pair of brain and heart

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ABSTRACT

Background: Takotsubo cardiomyopathy (TTC) is often triggered by emotional or physical stress factors. Psychological variables can have an impact on the physical manifestations of heart disease. TTC may reflect stunned myocardium from a neurogenic source. Anatomical connections between different parts of the brain can be visualized by diffusion tensor imaging (DTI) and thus, expressed by diffusion coefficient — fractional anisotropy (FA). A novel tool used to evaluate brain function in the absence of task is resting state functional magnetic resonance imaging (RS-fMRI).
Methods: The study included both psychological tests and RS-fMRI examination, and was performed uniformly, in patients with takotsubo and healthy controls. The final group of patients consisted of 13 women, each who underwent a typical pattern of TTC triggered by emotionally stressful factors. The control group included thirteen healthy, age-matched women.
Results: Psychological tests revealed that the Type D personality was not more likely to appear among studied patients with takotsubo cardiomyopathy than amongst the healthy population. However, the level of anxiety seen in patients with TTC was increased. There were no differences in FA values between patients and healthy controls. RS-fMRI showed that TTC patients had increased connectivity areas in the precuneus. The healthy controls, when compared to TTC patients had increased connectivity in the ventromedial prefrontal cortex.
Conclusions: Taking into account the RS-fMRI results, psychological testing may suggest that TTC patients place a greater focus on themselves (increased tendency to experience negative affectivity, greater conscientiousness) and might have problems with emotional control. Our findings lead to the hypothesis that there is a personality profile for TTC patients' reactions to stressful triggers.

1. Introduction

Takotsubo cardiomyopathy (TTC) is an increasingly recognized acute syndrome with symptoms similar to acute myocardial infarction (MI), mostly in the absence of obstructive coronary artery disease. TTC is a rare disease, affecting between 1.2% and 2.2% of people who suffer a myocardial infarction. It affects far more women than men, with over 90% of reported cases being women [1,2]. The syndrome is often triggered by emotional or physical stress factors and is characterized by reversible left ventricle wall motion abnormalities. The exact nature and relevance of triggering factors remain unclear.

Functional cardiac changes and ECG abnormalities observed in takotsubo cardiomyopathy may reflect activation of central neurogenic mechanisms [3]. Some body of literature stresses the fact of cardiac dysfunction accompanying cerebral pathologies [4]. Indeed, intracranial pathologies can produce the same myocardial histopathological findings found in takotsubo cardiomyopathy [5]. It is noteworthy, that cardiac sympathectomy prevents brain-mediated cardiac injury. Therefore, takotsubo cardiomyopathy may reflect stunned myocardium from a neurogenic source. Co-authors have recently described a signature of circulating microRNAs used for sensitive and accurate identification of TTC in the acute phase. This signature may become not only a valuable diagnostic tool for the immediate diagnosis of TTC, but also, the

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significant up-regulation of stress and depression-related microRNAs might suggest the role the central nervous system plays in TTC [6].

Psychological stress, personality, depression, and anxiety are amongst the psychosocial factors that have been associated with the pathogenesis and expression of heart disease [7–9]. Amongst these psychological variables, personality traits have been shown to have more explanatory power than the remaining factors. Personality traits have also been revealed to have significant meaning for patients with takotsubo syndrome, a fact was stressed in several studies [7,10]. Thus, our decision was to focus specifically on the Type D personality trait. Indeed, the Type D personality is thought to be a relatively stable trait that is characterized by a high negative affectivity (NA — the tendency to experience negative emotions such as dysphoria, anxiety, irritability, and a negative view of self) and social inhibition (SI — a tendency to inhibit the expression of emotions in social interactions or feeling inhibited, tense, and insecure when with others) [11]. In the literature, patients with a Type D personality have been shown to have a poorer prognosis following a myocardial infarction. In fact, Type D patients had a 4-fold increased risk of mortality, recurrent MI, or sudden cardiac death, independently of traditional risk factors [12,13]. It is possible that this personality trait plays a role in the pathogenesis of coronary heart disease. The Type D personality is also linked to clinical depression, which is frequently present in TTC patients [14]. However, psychological research about TTC reveals inconsistent results [7,8,15,16].

Diffusion imaging is an MRI method that produces in vivo magnetic resonance images of soft tissues by an MRI signal sensitized to water diffusion. In diffusion-weighted imaging (DWI), the intensity of each image element (voxel) reflects the rate of water random walk (diffusion) at that location. The displacement distribution profile of the water molecule diffusion can reveal microscopic details about tissue microstructure architecture. This, in turn, provides in unprecedented detail, the trajectories of white matter fibers in the brain, non-invasively [17]. The ability to visualize anatomical connections between different parts of the brain can be expressed by diffusion tensor imaging (DTI), and one of the most widely used, diffusion coefficient — fractional anisotropy (FA). Fractional anisotropy (FA) is a coefficient of anisotropy which assumes values between zero (which means that distribution is isotropic, unrestricted) and one (the diffusion is anisotropic, restricted). DTI has revolutionized our understanding of tissue injury in vivo, the development of white matter tracts, and functional connectivity within the brain [18].

A novel tool used in evaluating brain function is functional magnetic resonance imaging (fMRI) based on blood-oxygenation-level dependent contrast (BOLD). Initially, functional MRI was developed to measure changes in BOLD signal in specific brain regions, during the performance of a task or in response to a stimulus [19]. In recent years, the interest in the application of this technique essentially increased, but in the absence of a task, termed resting state functional magnetic resonance imaging (RS-fMRI). By using this type of imaging (RS-fMRI), certain regions of the brain, now called the Resting State Network (RSN), were proven to be active at rest, yet their activity decreased when a cognitive task was performed [20]. Perhaps the most fundamental RSN is the default mode network (DMN), which activates during silent brain or self-thinking. Key areas of the DMN are located in the posterior cingulate cortex (PCC)/precuneus and medial prefrontal cortex (MPFC). This network is considered to be responsible for spontaneous cognition, monitoring of the environment and also self-related thinking [21].

In the past few years, there has been a growing trend of resting-state fMRI use in patients with a variety of disorders, such as depression, autism, schizophrenia, attention deficit hyperactivity disorder and post-traumatic stress disorder [22–26]. The aim of our study was to evaluate the brain function in patients who suffered from TTC by use of RS-fMRI and various psychological tests.

To our knowledge, this is the first study evaluating brain resting state with these tools amongst patients with takotsubo cardiomyopathy.

Table 1
Clinical characteristic of the TTC study group.

Patients with TTC (n = 13)	
Mean age (years)	62 ± 7
LVEF (%)	67 ± 5
Hypertension, n (%)	5 (38)
Diabetes, n (%)	2 (15)
Current smoker, n (%)	4 (30)
Hypercholesterolemia, n (%)	7 (54)
HR (bpm)	72 ± 6
SBP (mm Hg)	123 ± 6
DBP (mm Hg)	83 ± 8

2. Methods

2.1. Study group

The study included both psychological tests and RS-fMRI examination, and was performed in patients with takotsubo cardiomyopathy and also in healthy controls. The study group consisted of sixteen women, all examined within 12–18 months since an acute episode of takotsubo cardiomyopathy. Each woman in the study group experienced the typical pattern of TTC (apical ballooning) triggered by emotionally stressful factors. The patients with takotsubo cardiomyopathy were diagnosed according to Mayo Clinic criteria and deemed fully recovered, with no ECG and left ventricle wall motion abnormalities. There was no history of stroke or any other neurological or psychiatric condition diagnosed after TTC onset. Clinical characteristics of the study group are outlined in Table 1. The final analyzed group consisted of thirteen subjects, as three examinations were excluded from the final analysis. Their exclusion was due to artifacts caused by head movement during fMRI acquisition, and thus, high-quality imaging was not obtained. Our study was approved by the local ethics committee, and each participant gave informed consent for testing.

The control group included thirteen healthy, age-matched women (TTC 62 ± 7 years vs. Controls 57 ± 5; p = 0.08) after the exclusion of three women due to their fMRI imaging studies not being suitable enough for further analysis. The controls have no signs or symptoms of any cardiovascular diseases. Also, there were no significant abnormalities seen in both resting transthoracic echocardiography and ECG. Individuals in the control group had no history of stroke, nor of any neurological or psychiatric conditions.

2.2. Psychological tests

To describe the patients' personalities, we chose to use the Big Five personality traits, which are measured by the NEO Personality Inventory by T. Costa and R.R. McCrae [27]. This questionnaire analyzes the five following factors: openness, conscientiousness, extraversion, agreeableness, and neuroticism. The Type D personality trait was measured with Denollet's questionnaire DS 14 [28]. This specific questionnaire analyzes Type D personality in regards to two independent dimensions — negative affectivity and social inhibition. Anxiety levels and depression were determined by The Hospital Anxiety and Depression Scale (HADS) from A. S. Zigmond and R. P. Snaith [29].

Psychological testing was qualitatively analyzed. Initially, the full scale of the measurement was unified by transforming the raw results into calculated data, that was then placed on the standardized scale (z-scores). The transformation was made based on the average and standard deviation of the control group. The ipsatization allowed for the observation of intraindividual variability possible. The tests were carried out according to the following criteria:

- results within the norm ($-1 \le z \le 1$)
- results beyond the norm* ($-2 \le z < -1$)
- results significantly beyond the norm ($z < -2$)

Because the number of results "significantly beyond the norm" was negligible, we decided to merge the "results beyond the norm" with the "results significantly beyond the norm."

2.3. MRI acquisition

MRI examinations were performed with Philips Achieva 3.0T TX (Philips, Best, The Netherlands) using the 32-channel head coil. The protocol included diffusion MRI sequence, and fMRI resting state sequence. The diffusion MRI was performed using echo planar imaging DTI sequence with 32 non-collinear gradient directions using b = 800 s/mm^2 and one b = 0 s/mm^2 (TR = 6900 ms, TE = 65 ms, voxel size 2 mm × 2 mm × 2 mm). The orientation was axial, and there were no angulations. The RS-fMRI scanning used a T2* gradient echo planar imaging sequence (FFE-EPI: TR = 2000 ms, TE = 30 ms, flip angle = 90°, voxel size 3 mm × 3 mm × 3 mm, 180 volumes, three dummy scans). The patients were asked to keep their eyes open and not to think of anything specific during the examination.

* The excessive intensity of the psychological trait or slightly intensity of the psychological trait (according to a scale in a particular test).