

## Peer Review File

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### Review Comments

Comment 1: Figures are missing from the paper.

Reply 1: Figures were assembled in the manuscript and also uploaded separately in the system.

Changes in the Text: See the bottom of the manuscript.

Comment 2: Providing the rs-fMRI graph may make the paper more convincing.

Reply 2: Figure1 to Figure 3 are the rs-fMRI graphs in the article and can demonstrate the abnormalities in rsFC. Due to the problem of project funds, no other graphs have been made yet.

Changes in the Text: See Figures 1 and 3.

Comment 3: What differences exist between GAD and major depressive disorder (MDD)?

Reply 3: Generalized anxiety disorder (GAD) is a persistent chronic excessive anxiety that is hard to control, and the main characteristics of GAD are chronic excessive anxiety and worry, which significantly affects the work efficiency and increases the risk for other diseases. Major Depressive Disorder (MDD) is a prevalent, chronic, disabling, and multidimensional mental disorder. Cognitive dysfunction represents a core diagnostic and symptomatic criterion of MDD, and is a principal determinant of functional non-recovery. Cognitive impairment has been observed to persist despite remission of mood symptoms, suggesting dissociability of mood and cognitive symptoms in MDD. GAD and MDD are both mental diseases, they are similar, but different. GAD may develop into MDD if not controlled.

Changes in the Text: We have deleted MDD in the article (see Page 17, line 22 to 25.)

Comment 4: What progress has been made in the treatment of GAD? Please include relevant content in the introduction.

Reply 4: Treatment for GAD often includes medications such as selective serotonin reuptake inhibitors and/or psychotherapy. Among psychotherapeutic treatments, cognitive behavior therapy has been studied widely and has an extensive evidence base. Benzodiazepines are effective in reducing anxiety symptoms, but their use is limited by risk of abuse and adverse effect profiles. Physical activity can reduce symptoms of GAD. Moreover, a number of complementary and alternative treatments are often used.

Changes in the Text: we added some data in our text as advised (see Page 4, line 8 to 13.)

Comment 5: What are the main components of Ningxin Anshen decoction?

Reply 5: The investigated product was NXAS Decoction, a Chinese herbal medicine product composed of Suan Zao Ren (equivalent to 60 g of crude drug/package), Ci Wu Jia (equivalent to 45 g of crude drug/package), and Xia Ku Cao (equivalent to 10 g of crude drug/package). NXAS Decoction was extracted from these three kinds of crude traditional Chinese medicine and made into granule mixture in Beijing Kangrentang Pharmaceutical Co., Ltd. The placebo, composed of dextrin, had the same appearance to NXAS Decoction. The participants in the NXAS group and placebo group were orally treated with 1 bag of NXAS Formula and placebo, respectively, twice daily (one in the morning and one in the evening) for 4 weeks.

Changes in the Text: we added the components of Ningxin Anshen decoction in our text as advised (see Page 9, line 1 to 9.)

Comment 6: The possible mechanism analysis should be increased. This would better support the conclusions of this study.

Reply 6: rsFC studies demonstrate abnormalities and mostly decreases in DMN in GAD. In contrast, resting-state fMRI shows increased rsFC in SN of GAD. Since rsFC is

coherence- or phase-based operating in the infraslow frequency domain (0.01-0.1 Hz), these data suggest spatiotemporal hypo- or hyper-synchronization in DMN and SN, respectively. These abnormalities in the neural network's spatiotemporal synchronization may, in turn, impact phase-based temporal synchronization of neural and cardiac activities resulting in decreased (DMN) or increased (SN) neuro-cardiac coupling in GAD. That, in turn, may be related to the various psychopathological symptoms like unstable sense of self (as based on unstable DMN showing spatiotemporal hypo-synchronization), increased emotions and specifically anxiety (as related to increased SN showing spatiotemporal hyper-synchronization) in GAD. Taken together, we here suggest altered spatiotemporal synchronization of neural and cardiac activity within the brain's resting state to underlie various psychopathological symptoms in anxiety disorders. Such spatiotemporal basis of psychopathological symptoms is well compatible with the recently suggested "Spatiotemporal Psychopathology." (50). And our study also revealed that the rsFC reduced in the DMN and increased in the SN of GAD patients, and self-designed NXAS decoction was able to increase the rsFC of PUCN and reduce the rsFC of orbIFG.L to relieve GAD, which may be one of mechanisms underlying the anti-anxiety effect of NXAS decoction.

Changes in the Text: we added some data in our text as advised ([see Page 17, line 6 to 24.](#))