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Baroreflex-mediated sympathetic overactivation induced by mental stress in post-traumatic stress disorder depends on the type of stressor

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Sympathetic overactivation has long been recognized as a deleterious condition, involved in the physiopathology of several diseases. The overactivity of the sympathetic nervous system (SNS) may be the consequence of different conditions and an intriguing question that still remains is whether diseases, such as hypertension and heart failure, are induced by increased SNS or increased SNS is a consequence of the disease progression. A reasonable assumption is that both statements can be correct, i.e. diseases might induce and be empowered by increased SNS.

Post-traumatic stress disorder (PTSD) is an example of a pathological condition associated to increased risk of cardiovascular events and hypertension. Previous studies have suggested that PTSD subjects present heightened sympathetic activity which could lead to this increased risk of cardiovascular disease. However, what is triggering the SNS overactivation in these subjects remains unclear. The arterial baroreflex, being strictly related to the regulation of SNS activity, might play a key role in the autonomic imbalance towards SNS overactivation. Thus, the assessment of baroreflex function could bring elucidative information on the sources of augmented SNS activity. For that reason, the baroreflex sensitivity (BRS) is broadly used as a marker of baroreflex functioning, so that decreased BRS points to an impaired baroreflex.

Recently in *The Journal of Physiology*, Park *et al.* (2017) published an interesting study contributing to our understanding of the mechanisms involved in increased cardiovascular risk in PTSD subjects. The authors tested the hypothesis that military war veterans with PTSD present greater SNS and haemodynamic reactivity in response not only to mental stress related to their trauma (virtual reality combat exposure; VRCE) but also to non-trauma-related mental stress (mental arithmetic; MA) when compared to matched control subjects. Park *et al.* (2017) also hypothesized that a baroreflex dysfunction might play a role in SNS overactivation during mental stress in PTSD subjects, increasing their risk of cardiovascular diseases and hypertension. In their study, for the first time, muscle sympathetic nerve activity (MSNA) was directly assessed in PTSD subjects during rest and mental stress conditions. The authors found that in response to VRCE, PTSD subjects showed significant increases in MSNA (quantified both as bursts frequency and total activity) and in heart rate when compared to matched control subjects. During MA, PTSD subjects presented greater increases in MSNA bursts frequency and in diastolic blood pressure in the first minute of the test. These data suggest that, although in a different pattern of response, PTSD leads to increased SNS and haemodynamic responses to mental stressors independently of whether they are related or unrelated to the trauma. Additionally, Park *et al.* (2017) assessed MSNA during a cold pressor test (CPT) that elicits a non-baroreflex-mediated SNS activation. The authors found that the increases in MSNA, blood pressure and heart rate were not different between PTSD and control subjects suggesting that the SNS overactivity in PTSD is restricted to mental stress conditions and, importantly, is baroreflex-mediated.

In order to confirm the influence of the baroreflex on the increased SNS and haemodynamic responses to mental stress in PTSD subjects, the authors assessed sympathetic and cardiac BRS at rest and during VRCE. Both sympathetic and cardiac BRS were found to be decreased in PTSD subjects at rest when compared to control subjects. However, during VRCE only cardiac BRS was reduced in PTSD subjects. Although further tests conducted with bigger samples are still needed, these results strongly suggest that baroreflex dysfunction is an underlying mechanism triggering SNS increased reactivity to mental stress in PTSD. Finally, Park *et al.* (2017) found that baseline highly sensitivity C-reactive protein (hsCRP) is increased in PTSD in comparison to control subjects, proposing that inflammation could be a potential mechanism leading to baroreflex dysfunction and increased SNS responses to mental stress.

The data presented by Park *et al.* (2017) bring clear-cut evidence that baroreflex dysfunction plays an important role in PTSD as in many other diseases where there is an autonomic imbalance. In PTSD, an impaired baroreflex seems to be triggering the overactivation of the SNS in response to mental stress, which in turn increases the risk of cardiovascular events and other diseases, such as hypertension. In the majority of analyses of the baroreflex, it is common to find its function evaluated solely by BRS. In fact, BRS is a valuable index of baroreflex function as it measures the magnitude of the responses elicited by the baroreflex when there is a 1 mmHg change in arterial pressure. However, another meaningful index of baroreflex function that is usually overlooked is the baroreflex effectiveness index (BEI), which can bring additional information, complementary to BRS. While BRS is related to the magnitude of the baroreflex responses, the BEI measures how much of the stimuli is being transduced into a response. In other words, BEI is the percentage of change in arterial pressure that is effectively transmitted through the neural pathways to a reflex response (changing, for example, heart rate or MSNA) (Di Rienzo *et al.* 2001).

To illustrate the importance of BEI, it was recently shown that in rats with early heart failure, the BRS of renal sympathetic nerve activity is not altered, compared to controls. However, the BEI of rats with early heart failure is half the BEI of controls, indicating that although the sensitivity is the same, the effectiveness of the baroreflex to respond to changes in arterial pressure is affected (Lataro *et al.* 2017). We believe that subjects with PTSD might have a decreased BEI, compared to controls, as not only decreased sensitivity (BRS) but also the failure to respond to some of the pressure stimuli (BEI) may be associated to SNS overactivity during mental stress.

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On the one hand the BEI could add value and consolidate the findings presented by BRS. On the other hand the BEI could be elucidative and clarify whether or not the baroreflex is impaired even when BRS is not altered. This could be the case, for example, when subjects were submitted to combat-related mental stress (VRCE) in the study of Park *et al.* (2017), where sympathetic BRS was not found to be different between PTSD and controls. Possibly, BRS and BEI are indices related to distinct pathways within the neural baroreflex regulatory system, and as such, they are important in the understanding of the associated diseases.

It is also worth noting the probable involvement of the limbic system during VRCE-induced responses shown in the study of Park *et al.* (2017). VRCE evoked traumatic memories in PTSD subjects, activating limbic regions such as hippocampus and amygdala, directly involved in fear/trauma-related information processing. These regions were found to modulate the hypothalamus–pituitary axis and the autonomic nervous system by sending projections to the hypothalamus and to other preautonomic areas (Ulrich-Lai & Herman, 2009), affecting SNS output and/or its regulation by the baroreflex. Thus, this could help to explain the significant increase in MSNA and heart rate that was observed in PTSD but not in control subjects during VRCE in the study of Park *et al.* (2017). Additionally, the assumption that the different mental stressors – VRCE and MA – recruited different brain regions should be taken into consideration. It is likely that MA, instead of the limbic system, predominantly activated cortical regions such as the prefrontal and parietal cortices, affecting the SNS output and regulation in a different manner. This could be another potential explanation of the different patterns of response caused by VRCE and MA in the study of Park *et al.*

In conclusion, Park *et al.*'s study represents a step forward in understanding the mechanisms involved in the higher cardiovascular risk in PTSD. The data presented by the authors showed that a decreased BRS contributes to an SNS hyperactivation during different mental stress situations. Also, they suggested that chronic inflammation could be one possible factor causing BRS impairment and could contribute to increasing the central SNS output. In addition to their findings, we suggest that useful and complementary information could be extracted from the BEI, which provides a different view of the baroreflex function by measuring whether the changes in arterial pressure are, in fact, transduced into reflex homeostatic responses. Moreover, we have highlighted the potential role played by different brain regions in generating and modulating the SNS activity during the different types of mental stress (VRCE and MA). Considering all of these potential mechanisms, future studies should be directed to investigating what is triggering the decreased BRS and the exacerbated sympathetic reactivity in response to distinct mental stressors in PTSD subjects. The findings will contribute to the development of therapeutic strategies targeting the primary causes of cardiovascular risk in PTSD.

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Additional information

Competing interests

None.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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