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SHORT COMMUNICATION

A mosaic of sex-related structural changes in the human brain following exposure to real-life stress

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Abstract

Whereas sex differences in the brain's response to stress have been reported in both humans and animals, it is unknown whether they 'add up' consistently within individual brains. Here, we studied this question in a unique data set of magnetic resonance imaging (MRI) scans obtained before and after exposure to extreme real-life stress in the form of combative military service in 34 (15 women) young (18–19 years old) healthy soldiers. Across two data sets, one of regional volume and one of cortical thickness, only a few regions (seven and three, respectively) showed sex/gender-specific changes (i.e., the most common structural change in women and men was different). The number of internally consistent brains (a male-typical or a female-typical response in all regions) was not different from the number expected by chance nor from that observed in regions showing a sex-similar response, and was lower than the number of mosaic brains (at least one region with a male-typical response and one with a female-typical response). Although these findings do not reveal the source of sex/gender differences in response to stress and of within-brain variability in this response, they demonstrate that these differences do not consistently add up to create a female-typical and a male-typical neural response to stress.

Keywords Combat-related stress · Sex differences · Gender differences · MRI

Introduction

Response to stress is a vastly studied field (for reviews, see Ganster and Rosen 2013; Robinson 2018) due to its often detrimental physiological and psychological consequences (for review, see Admon et al. 2013b; Slavich 2016). Traumatic experiences are thought to have long-lasting effects on brain structure and function (for review, see Bremner 2006; Stark et al. 2015). Sex differences have been reported in the neural consequences of exposure to stress in animals (for review, see McLaughlin et al. 2009; Maeng et al. 2010; Shors 2016), and there is also some evidence for sex/gender differences in stress-related alterations in the macrostructure of gray matter in humans (Teicher and Samson 2016; Klabunde et al. 2017). It is unknown, however, whether sex/gender differences in response to stress 'add up' consistently within individuals—that is, all changes are in the direction typical of women or all are in the direction typical of men, or whether the response to stress of each individual consists of a 'mosaic' of both male-typical and female-typical responses.

The aim of the present study was to test this latter question in a unique data set of magnetic resonance imaging (MRI) scans that were obtained before and after exposure to extreme real-life stressful events. Thirty-four healthy young (18–19 years old, 15 women) soldiers underwent scanning during their first week of a pre-military paramedic preparation course (Before Stress) and 36 months later, at the end of their military service as combat paramedics in various fighting units (After Stress). During their military service, all

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participants experienced at least one highly stressful event during which they were exposed to the sights of severe causalities and had to treat patients with severe injury. These experiences were similarly accompanied in men and women by intense negative emotions and an increase in stress-related behavioral symptoms (Admon et al. 2009, 2013b, c).

To test the mosaic hypothesis, we first identified regions in which structural changes (either an increase or a decrease in volume or in cortical thickness) from the Before Stress to the After Stress time points, which were most common in one sex, were different from those most common in the other sex (i.e., either a change in the opposite direction or no change). Next, we tested within each individual whether their stress-related structural changes in these regions were internally consistent (i.e., all regions responded in the way typical of women, or all responded in the way typical of men) or mosaic (i.e., at least one region responded in the way typical of women and at least one other region responded in the way typical of men). Finally, we compared internal consistency in stress-related responses in these regions (i.e., regions that showed a sex-specific response) to that observed in regions that showed a similar stress-related response in women and men (sex-similar response).

Materials and methods

Data collection and preparation for analysis

For the full details of the participants and of the imaging protocols, see Admon et al. (2013a).

Participants The study group comprised 34 (15 women) 18-year-old soldiers recently drafted to mandatory military service to serve as combat paramedics in the IDF. Only individuals that reported no history of psychiatric disorders for them and their families and no traumatic experiences before recruitment were selected to participate in the study. All participants provided written informed consent approved by the Tel Aviv Sourasky Medical Center Ethics Committee.

MRI Data Acquisition Participants were scanned during their first week of the pre-military paramedic preparation course and 36 months later. At both time points, MRI scans were performed on a 3.0-T MRI scanner (GE Signa EXCITE, Milwaukee, WI) with a standard eight-channel head coil. Identical anatomical 3D spoiled gradient-echo sequences for the whole brain were obtained with high-resolution isotropic 1-mm slice thickness field of view (FOV): 25X18; matrix: 256X256; and TR/time echo (TE): 7.3/3.3).

Surface-based analysis The FreeSurfer software package (Athinoula A. Martinos Center for Biomedical Imaging, Harvard University, Cambridge, MA, USA; http://surfer.nmr.mgh.harvard.edu/fswiki) was used to generate the surface representations of the cortex and to delineate 68 regions (Fig. 1a). For each participant, we calculated the average cortical thickness (gray–white matter boundary to pial boundary) and total cortical volume for each of these regions, as well as the volumes of 26 subcortical structures (Fischl et al. 2004; Desikan et al. 2006).

Analysis

Two data sets, one of cortical thickness and the other of regional volume, were analyzed separately. In each data set, the percent of change between the first and second time points that constitutes an increase, a decrease or no change was determined on the basis of variability of the percent of change in regions that showed a non-significant average change smaller than 1% (Fig. 1b, c). Next, in each data set, regions were chosen for the sex-specific response analysis if the response to stress most common in women was different from the response most common in men, and the Sex x Time interaction for the region was significant ($p < 0.05$). Internal consistency and mosaicism in the response to stress among these regions were assessed for each individual brain (Fig. 1d, e). In addition, on the basis of the percent of individuals showing a sex-typical response in each region, we calculated the percent of brains that are expected to be internally consistent under conditions of perfect internal consistency and under conditions of perfect independency between regions (for details, see Supplementary Materials).

Regions were marked as showing a sex-similar response if the response to stress (a decrease or an increase) most common in women was the same as the response most common in men, and the effect of Time but not the Sex x Time interaction was significant. Of these regions, we chose for the analysis of internal consistency those in which the percent of participants with the most common response was similar to the percent of participants with the most common response in one of the sex-specific regions (for details, see Supplementary Materials). Internal consistency was assessed for each individual brain over all possible combinations of these regions (see Supplementary Materials).

Data availability

The data analyzed here are available on request from the corresponding author.

Results

Table 1 presents for each data set the number of regions included in the analysis, the number of regions that changed differently in women and men (sex-specific), the number of regions that changed similarly in women and men, and the number of regions included in the sex-similar analysis (in

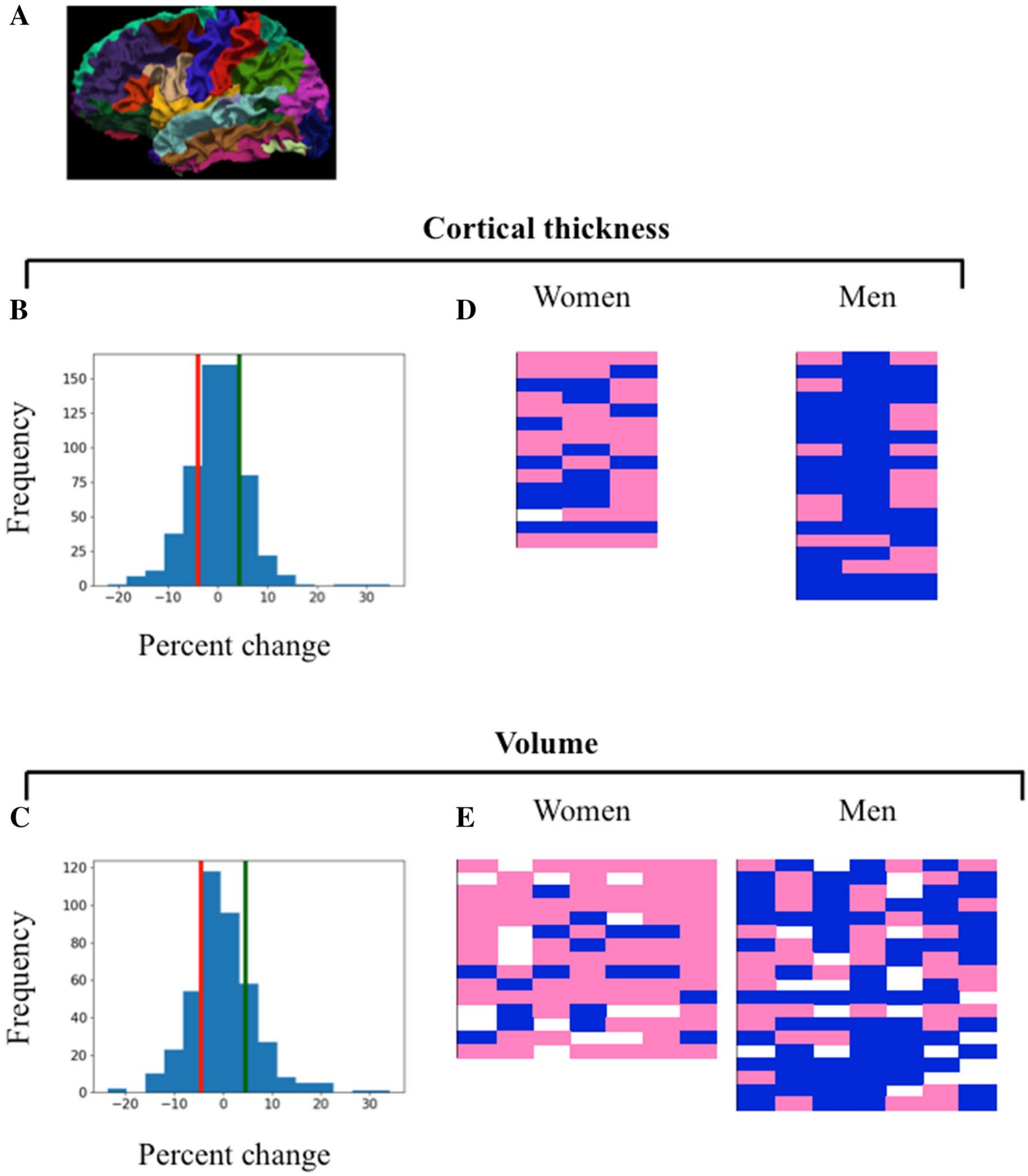

Fig. 1 **a** Sixty-eight cortical regions were delineated using the FreeSurfer software package (the picture was reproduced with permission from https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/AnatomicalROI). We calculated for each participant the average cortical thickness and the total cortical volume for each of these regions, as well as the volumes of 26 subcortical structures. **b**, **c** The distribution of the percent of change in cortical thickness (**b**) and in volume (**c**) of all regions in which the average change was smaller than one percent. Scores falling above the 80 percentile (marked in green) were treated as an increase, and those falling below the 20 percentile (marked in red) were treated as a decrease. **d**, **e** For each of the regions showing a sex-specific response to stress, female-typical responses are marked in pink, male-typical responses are marked in blue, and the response which was not typical of either sex is marked in white. *D* cortical thickness, *E* regional volume. The order of regions in the two tables is the same as in Table 2

brackets). Table 2 lists the regions that showed a sex-specific and a sex-similar response (regions that were included in the sex-similar analysis are marked with an asterisk). Supplementary Table S1 presents the number of regions used to delimit what constitutes a change; the percent of change that constitutes a decrease and an increase; and the average percent of participants with the most common response over the regions included in the sex-specific and sex-similar analyses.

Table 1 Summary of results

Dataset	Sex-specific regions	Sex-similar regions (in analysis)	Number of mosaic brains (percent of sample)	Number of internally consistent brains (percent of sample)	Expected percent of internally consistent brains under independence (%)	Expected percent of internally consistent brains under full dependence (%)	Percentile in distribution of internally consistent brains in sex-similar analysis (%)
Cortical thickness (68 regions)	3	10 (4)	22 (64.7%)	11 (32.4%)	30.3	70.6	0
Volume (94 regions)	7	20 (11)	25 (73.5%)	1 (2.9%)	3.3	61.8	62.5

Table 2 Regions showing a sex-specific or a sex-similar response to stress

Area	Hemisphere	Cortical thickness	Volume
Sex-specific			
Pars opercularis	Right	F ↓ M -	
Lateral occipital	Right	F – M ↑	
Lateral occipital	Left	F – M ↑	
Inferior parietal	Right		F – M ↓
Inferior parietal	Left		F – \M ↓
Pericalcarine	Right		F – M ↑
Pericalcarine	Left		F –M ↑
Corpus callosum—central	N/A		F↓ M ↑
Corpus callosum—mid-anterior	N/A		F ↓ M –
Corpus callosum—anterior	N/A		F ↓ M –
Sex-similar			
Accumbens area	Left		↑
Brain Stem	N/A		↓
Cerebellum Cortex	Left		↓
Fusiform	Left		↑
Fusiform	Right	↑	↑
Inferior temporal	Right	↑	↑
Lateral occipital	Left		↑
Lateral occipital	Right		↑
Lateral orbitofrontal	Left	↓	
Lateral orbitofrontal	Right	↓	
Lingual	Left		↑
Medial orbitofrontal	Right	↓	↓
Middle temporal	Left		↑
Middle temporal	Right		↑
Parahippocampal	Right	↓	↓
Pars orbitalis	Right	↓	
Pars triangularis	Right	↓	↓
Pars triangularis	Left	↓	↓
Right cerebellum white matter	Right		↑
Rostral middle frontal	Right	↓	↓
Transverse temporal	Left		↓
Transverse temporal	Right		↓
Ventral DC	Right		↓

As can be seen in Tables 1 and 2, following exposure to extreme real-life stress, the soldiers exhibited many brain structural changes (both increases and decreases in regional volume and in cortical thickness), in both women and men; with a total of 31 regions (over the two types of measures, cortical thickness and regional volume) showing significant structural changes. In ten of these regions, the direction of structural changes was sex-specific. Of these ten, the central region of the corpus callosum was the only region in which the most common response was opposite in men and women, whereas in the other nine regions, the most common response in one sex was a decrease or an increase, whereas the most common response in the other sex was no change (in six regions a decrease or an increase was observed in men but not in women, and in three regions, a change was observed in women but not in men).

Table 1 and Fig. 1d, e present the results of the internal consistency analysis of the sex-specific response to stress. In the two data sets, the number of internally consistent brains was lower than the number of mosaic brains. Moreover, the proportion of internally consistent brains was not statistically different from the proportion expected if the response to stress of different regions was independent, but significantly lower from the proportion expected if the response to stress of different regions was fully consistent. Finally, the number of internally consistent brains in the sex-specific response to stress was lower than the number of internally consistent brains in the sex-similar response to stress in all runs of the sex-similar control analyses of the cortical thickness data set, and in 37.5% of the runs of the sex-similar control analyses of the volume dataset. In other words, the degree of internal consistency in sex-specific responses to stress was not greater than the degree of internal consistency in the response to stress that was not sex-specific.

Discussion

The present study revealed structural alterations following exposure to severe real-life stress in many brain regions that were previously implicated in the response to stress in cross-sectional studies, including the hippocampal complex, anterior cingulate cortex, prefrontal, temporal and occipital cortical regions, insula, cerebellar regions, striatum, and brainstem (Pitman et al. 2012; Tavanti et al. 2012; Admon et al. 2013a; Tan et al. 2013; Li et al. 2014; Cheng et al. 2015; Meng et al. 2016; Sussman et al. 2016; Klabunde et al. 2017).

The finding of group-level sex/gender differences in the response to stress in some brain regions in the present study is in line with the previous reports in both humans (Teicher and Samson 2016; Klabunde et al. 2017) and animals (for review see, McLaughlin et al. 2009; Maeng et al. 2010; Shors 2016) of sex differences in the effects of stress. It is possible that with a larger sample, more regions showing sex/gender differences in response to stress would have been detected. Future studies may unravel the source of these differences, that is, whether they reflect biological (e.g., genes, hormones) or socio-cultural factors (e.g., gender roles, socioeconomical status) associated with being male or female (Joel and Fausto-Sterling 2016; Joel and McCarthy 2017).

The present study is the first to move from the group level to the individual level, and assess internal consistency in the sex-specific responses to stress. This analysis revealed that sex-specific responses do not consistently add up in the brain of individual women and men. This lack of internal consistency is evident in two observations. The first is that the prevalence of brains that were internally consistent in their sex-specific response to stress was not higher than the prevalence expected by chance, but was much lower than the prevalence expected if the sex-specific response to stress was consistent across brain regions. The second observation is that the prevalence of internal consistency in sex-specific responses to stress was not greater than the prevalence of internal consistency in the response to stress that was not sex-specific.

Our study does not reveal the source of this within-brain variability in the response to stress, but this variability is in line with animal studies, showing that sex effects are exerted via multiple independent mechanisms and may vary according to internal and external factors (for review, see McCarthy 2016). One possibility is that different sex/gender-related biological or socio-cultural factors are mediating sex/gender effects on each of the regions; another possibility is that the same sex/gender-related factor is affecting several regions, but its effects on each region are differently influenced by other internal or external factors or overshadowed by the effects of other factors. Note that within-brain variability in the response to stress is not unique to regions showing a sex/gender difference in their response, but was also seen in regions showing a similar response in women and men.

The present analysis also revealed a high number of mosaic brains, that is, brains with a combination of female-typical and male-typical responses. This finding extends the observation that mosaicism is more common than internal consistency in brain structure (Joel et al. 2015) to the realm of stress-induced structural alterations. These findings demonstrate that even though there are group-level sex/gender differences in response to stress, they do not add up to create a 'male-typical' (i.e., common in men) and a 'female-typical' response to stress.

The present study reveals that there are many similarities and some differences in structural changes in the brain following exposure to severe real-life stress, and that the differences mix up in individual brains. It follows that while sex category should surely be one of the factors taken into account in stress research, the binary approach should be replaced by one that appreciates the complex ways in which sex/gender-related effects mix up in individuals.

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Compliance with ethical standards

Conflict of interest The authors report no competing interests.

Ethical statement All procedures were in accordance with the ethical standards of the institutional committee (Tel Aviv Sourasky Medical Center Ethics Committee, 05-262) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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