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A longitudinal resting-state functional connectivity analysis on trauma exposure and post-traumatic stress symptoms in older individuals

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ABSTRACT

Background: Given the present demographic shift towards an aging society, there is an increased need to investigate the brain's functional connectivity in the context of aging. Trauma exposure and post-traumatic stress disorder (PTSD) symptoms are factors known to impact healthy aging and have been reported to be associated with functional connectivity differences. In the present study, we examined and compared differences in within-Default Mode Network (DMN), within-Salience Network (SN) and between DMN-SN functional connectivity, between trauma-exposed individuals with and without PTSD symptoms as well as non-traumatized individuals in a non-clininical older adult sample. METHODS: Resting state functional MRI and behavioral data is taken from the Longitudinal Healthy Aging Brain Database Project (LHAB). For the present analysis, participants who completed the questionnaires on trauma exposure and PTSD symptoms ($N = 110$ individuals of which $n = 50$ individuals reported previous trauma exposure and $n = 25$ individuals reported PTSD symptoms; mean age = 70.55 years, $SD = 4.82$) were included. RESULTS: The reporting of PTSD symptoms relative to no symptoms was associated with lower within-DMN connectivity, while on a trend level trauma-exposed individuals showed higher within-SN connectivity compared to non-trauma exposed individuals. Consistent with existing models of healthy aging, between DMN-SN functional connectivity showed an increase across time in older age. CONCLUSION: Present results suggest that alterations in within-DMN and within-SN functional connectivity also occur in non-treatment seeking older adult populations with trauma exposure and in association with PTSD symptoms. These changes manifest, alongside altered between DMN-SN functional connectivity, in older age supposedly independent of aging-related functional desegregation.

1. Introduction

During the past years there has been a growing interest in investigating intrinsic connectivity networks (ICN) to study the brain's intrinsic organization across different brain developmental and older age stages (Damoiseaux, 2017; Sullivan et al., 2019; Qiao et al., 2019). Within the context of aging, it is suggested that the organization of the brain's ICN changes as a function of aging particularly in later life periods. From pertinent studies, of which most are cross-sectional in nature, evidence was derived for lower functional connectivity within several ICNs (e.g., default mode, frontoparietal control and salience ventral attention network) and higher functional connectivity between networks in later decades of life as compared to the whole adult lifespan – changes that lead to desegregation of functional networks in older age (Jockwitz & Caspers, 2021; Malagurski et al., 2020; Setton et al., 2021). Given the stated ICNs association with aging and the fact that more and more adults reach later life stages (Fuster, 2017; Phillips and Gyasi, 2021), it is of outmost importance to further our understanding on how the brain's intrinsic organization changes by age and which factors may have an impact on differential aging trajectories.

One factor that is thought to meaningfully influence aging trajectories with respect to intrinsic connectivity is the exposure to current or past traumatic events (Cook & Simiola, 2018). So far, however, the majority of research on trauma exposure has been conducted in adolescence and young to middle aged adults (López et al., 2017; Sowder et al., 2018) and there exists only ample evidence for long(er)-term health and brain functioning outcomes following trauma exposure in older age (Reuveni et al., 2016; Szeszko & Yehuda, 2019). Hence,

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an interesting path to follow is the investigation of trauma exposure in older individuals, who may have also had a higher chance of having been exposed to traumatic events in their earlier life (Glaesmer et al., 2010). This is further of interest since post-traumatic stress disorder (PTSD) symptoms, as the most prevalent subsequent psychopathology, may manifest differently in older adults (Maercker, 2021). More precisely, epidemiological studies have shown that the prevalence of past year PTSD is significantly lower for older adults as compared to younger and middle-aged adults and is most likely to unfold in a subthreshold representation of PTSD symptoms (de Vries & Olff, 2009; Reynolds et al., 2016). Although not meeting full diagnostic criteria for PTSD, older individuals' health and brain functioning may still be meaningfully affected by symptoms on a subthreshold syndromale level (Pietrzak et al., 2012). Hence, there is much to suggest to also thoroughly examine the impact of trauma exposure and PTSD symptoms on ICNs in non-clinical older adult populations.

Up until now, our understanding of ICNs in trauma-exposed individuals and PTSD symptoms is primarily based on studies using clinical populations. On the basis of resting-state functional Magnetic Resonance Imaging (rs-fMRI), a method that is commonly used to measure resting-state functional connectivity (rs-FC) within and between ICNs, differences between trauma-exposed individuals with and without PTSD within and between ICNs (Fu et al., 2019; Garrett et al., 2019; Misaki, et al., 2018) have been revealed. More precisely, two ICNs have been of particular interest in this area of research: a) the default mode network (DMN), implicated in internally directed cognition (Buckner and DiNicola, 2019), and b) the salience network (SN), responsible for evaluating the valence of incoming stimuli (Uddin, 2015). However, so far no consensus exists whether the brain's intrinsic connectivity patterns are sensitive to trauma exposure per se or if changes in ICNs are related to the presence of PTSD symptoms (Lokshina et al., 2021).

For instance, in a study adressing consequences of early-life trauma, individuals suffering from chronic PTSD showed lower within-DMN rs-FC compared to non-trauma exposed controls (Bluhm et al., 2009). Other studies compared trauma-exposued individuals with and without PTSD to non-trauma exposed controls. Whilst one study observed reduced within-DMN rs-FC in individuals with trauma-exposure with and without PTSD compared to non-traumatized controls (DiGangi et al. 2016), another study observed lower within-DMN rs-FC in individuals reporting PTSD as compared to non-trauma exposed controls, but no differences between trauma-exposed individuals and non-trauma exposed controls (Sheynin et al. 2020), suggesting abbarrent within-DMN rs-FC predominantly in individuals with PTSD symptoms.

In the same vein, previous research findings declare the SN to be hyperconnected in PTSD and/or trauma-exposed individuals (Sripada et al., 2012). However, here differences in the brain's intrinsic organization are thought to stem from a different course of action. More precisely, previous studies have shown that individuals with prior trauma exposure (with or without PTSD symptoms) display greater within-SN rs-FC as compared to non-trauma exposed controls (Chen et al., 2019; Sheynin et al., 2020; Stark et al., 2015), translating into the assumption that trauma exposure alone and not the manifestation of PTSD symptoms contributes to abbarent within-SN rs-FC.

Additionally, there are mixed findings with regard to between-network (DMN-SN) rs-FC. While in some studies individuals with PTSD exhibited greater cross-network functional connectivity between DMN and SN in comparison to non-trauma exposed controls (Block et al., 2017; Sripada et al., 2012; Zhang et al., 2015), another study observed lower connectivity between the DMN and attentional control networks in individuals with PTSD (Patriat et al., 2016). Further, when comparing trauma-exposed individuals with and without PTSD and non-trauma exposed individuals, only those suffering from PTSD symptoms and neither trauma-exposed nor non-trauma exposed individuals showed DMN-SN desegregation (Sheynin et al., 2020). Hence in order to improve our understanding regarding ICN changes following trauma exposure and the neurogenesis of PTSD a threefold group differentiation (e.g., individuals with PTSD, trauma-exposed individuals without PTSD and non-trauma exposed controls), may be crucial in future investigations (Abdallah et al., 2019; Sripada et al., 2012).

Beyond the levels of within- and between-network rs-FC, our knowledge is very limited when it comes to the question whether true within-person change of rs-FC is affected by trauma exposure or PTSD symptoms. Most of the research has been cross-sectional and longitudinal studies have primarily been conducted to measure functional abnormalities prior and post PTSD therapy (Zhou et al., 2012). To the best of our knowledge, there have not been any published longitudinal rs-FC studies on trauma exposure and PTSD symptom-related changes in a non-clinical older adult sample (>65 years).

As such, our aim, which was also preregistered prior to performing any analysis (https://osf.io/3yztu), was to investigate and compare rs-FC within and between ICNs as well as longitudinal change in these metrics in non-clinical older individuals (a) with prior trauma exposure and PTSD symptoms, (b) with prior trauma experience but no PTSD symptoms and (c) with no trauma exposure. We hypothesized that, in the present non-clinical sample, individuals with prior trauma exposure compared to non-trauma exposed individuals, a) display greater within-SN connectivity but do not show aberrant within-DMN or between-network connectivity, and b) display greater enhancement of within-SN connectivity across time but not with regard to within-DMN or between-network connectivity. Further, we hypothesize that individuals with PTSD symptoms compared to those without, c) show weaker within-DMN connectivity, stronger within-SN and greater between DMN-SN connectivity, and d) display decline of within-DMN connectivity across time as well as an enhancement of within-SN and between DMN-SN connectivity across time.

2. Methods

2.1. Participants

Neuroimaging data from five measurement occasions (i.e., baseline, 1-year follow-up, 2-year follow-up, 4-year follow-up, 7-year follow-up) were taken from the Longitudinal Healthy Aging Brain Database Project (LHAB; Switzerland) conducted at the University of Zürich (Zöllig et al., 2011). At each measurement, participants underwent brain imaging, performed a battery of psychometric cognitive and motor ability tests and completed different questionnaires. Inclusion criteria for study participation at baseline were age $\geq$ 64, right-handedness, fluent German language proficiency, a score of $\geq$ 26 on the Mini Mental State Examination (MMSE; Folstein et al., 1975), no self-reported neurological disease of the central nervous system and no contraindications to MRI. The study was approved by the ethical committee of the canton of Zürich and all participants gave informed consent in accordance with the declaration of Helsinki.

For the present analysis, only participants who completed questionnaires on trauma exposure and PTSD symptoms, which were administered at the 4-year follow-up occasion, were included, resulting in a sample of $N = 110$ individuals of which $n = 50$ individuals reported previous trauma exposure and $n = 25$ individuals reported PTSD symptoms. The full sample (including individuals with and without trauma exposure) had a mean age of 70.55 years ($SD = 4.82$) with 50% of the sample being female ($n = 55$). The level of education was assessed on a scale from 1 to 3; 1 = high school with or without vocational education ($N = 33$), 2 = higher education entrance qualification, business school or university of applied sciences ($N = 22$), or 3 = university degree ($N = 55$). Further socio-demographic information are displayed in Table 1.

2.2. Trauma exposure and post-traumatic stress measure

The 7-item Short Screening Scale for DSM-IV Posttraumatic Stress

Table 1
Sample characteristics.

	Entire sample (N = 110)	Individuals with trauma exposure (n = 50)	Individuals with trauma exposure and PTSD symptoms (n = 25)
M_{age} (*SD*)	70.55 (*4.82*)	70.89 (4.96)	71.26 (5.05)
Sex *n* (%)			
Female	55 (50)	28 (56)	13 (52)
Male	55 (50)	22 (44)	12 (48)
Education *n* (%)			
High school	33 (30)	14 (28)	6 (24)
Higher education	22 (20)	11 (22)	7 (28)
University degree	55 (50)	25 (50)	12 (48)

Note. M_{age} = mean age, *SD* = standard deviation, *N*/*n* = number of individuals, PTSD symptoms = individuals with post-traumatics stress disorder symptoms.

Disorder (Breslau et al., 1999; Siegrist & Maercker, 2010) was used to screen for trauma exposure over the life course and presence of PTSD symptoms within the last month. The inventory measures the frequencies of seven PTSD symptoms within the last months: intrusions, flashbacks, nightmares, avoidance internal, avoidance external, hypervigilance and exaggerated startle response. Regarding trauma exposure, a total of eight different types of traumatic events were assessed using the trauma exposure items of the DIA-X interview (Wittchen & Pfister, 1997): war experience, physical abuse, sexual abuse, sexual abuse in childhood, natural disaster, serious accident, imprisonment, witness of a traumatic event. Regarding the frequency of exposure to a traumatic event and the distribution of PTSD symptoms: a total of $n = 60$ individuals reported to not have been exposed to a traumatic event, while $n = 50$ individuals reported that they have been exposed to at least one traumatic event in their lives. For the symptom prevalence, of the $n = 25$ individuals reporting PTSD symptoms, $n = 17$ (68%) reported intrusions, $n = 10$ (40%) nightmares, $n = 10$ (40%) flashbacks, 11 (44%) internal avoidance, $n = 6$ (24%) external avoidance, $n = 5$ (20%) hypervigliance when reminded and $n = 7$ (28%) exaggerated startle response.

2.3. MRI acquisition

MRI scanning was performed on a Philips 3 T Ingenia Medical Scanner with a 32-channel head coil and comprised T1-weighted anatomical scans (160 slices; TR 8.1 ms, TE 3.7 ms, FOV 240 × 240, 160 mm, flip angle 8°, isotropic voxel size 1.0 × 1.0 × 1.0 mm3) and T2* weighted rs-fMRI scans (gradient echo-planar sequence; transverse slice orientation; 43 slices; voxel size: 3.5 × 3.5 × 3.5 mm3; TR 2000 ms; TE 21 ms; flip angle 76°; FOV 220 × 220 × 150 mm). For the rs-fMRI scan, for which the acquisition time was within 8 min, participants were instructed to lie relaxed, while keeping their eyes open.

2.4. MRI preprocessing

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 20.1.3 (Esteban et al., 2019), which is based on *Nipype* 1.5.1 (Gorgolewski et al., 2011, 2018). Briefly, we used a preprocessing pipeline suitable for longitudinal data which included the following steps: bias field correction, skull stripping, brain tissue segmentation, slice time correction, correction for head motion parameters, co-registration to corresponding structural image, and non-linear spatial normalization to MNI space. The full report on anatomical and functional data preprocessing can be found in Supplementary Material.

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 (Abraham et al. 2014), mostly within the functional processing workflow. For more details of the pipeline, see https://fmriprep.readthedocs.io/en/stable/workflows.html.

Correlation matrices were estimated with the *nilearn* Python package (v. 0.7.0; Abraham et al., 2014). To remove physiological and other sources of noise from the fMRI time series, nuisance covariates we regressed out according to the 36-parameter model (Ciric et al., 2017). The fMRI confounds generated with fMRIprep were loaded using the *load_confound* (v. 0.6.4.) Python package. Six motion parameters, signals estimated from cerebrospinal fluid (CSF) and white matter (WM), the whole-brain global signal, their derivatives, quadratic terms, and squares of derivatives were regressed out from functional data separately for each run. The rs-fMRI data was temporally bandpass filtered in the 0.01 – 0.1 Hz frequency range. Global signal regression (GSR) was performed in line with previous studies on healthy aging (Chan et al., 2014; Malagurski et al., 2020; Ng et al., 2018), as this has been shown to be effective in minimizing the effects of physiological noise and head motion. Further, we used mean framewise-displacement (FD) (Power et al., 2012) as a quality assurance parameter. More specifically, fMRI data were identified as being of low quality if mean FD values exceeded three median absolute deviations (MADs) above the median of the sample distribution across measurement occasions. In total, $n = 18$ scans were excluded, all of which pertained to individuals with trauma exposure.

2.5. Region and network definition and extraction of connectivity metrics

The DMN and SN were defined using the Schaefer et al. (2018) parcellation, in which 100 parcels are assigned to 7 well-known resting state networks according to the Yeo-Krienen atlas (Yeo et al., 2011).

Connectivity matrices for each participant and measurement occasion were computed with pairwise correlation between average time series extracted from selected regions. These correlation coefficients were then transformed to z-values using the Fisher's r-to-z transformation.

The DMN comprised the following regions in both hemispheres: parietal cortex, temporal cortex, prefrontal cortex (ventral, dorsal, medial) and precuneus-posterior cingulate cortex. The SN included the right tempro-occipital-parietal region, right frontal-operculum-insula and right medial nodes and left frontal-operculum-insula, left parietal operculum, left prefrontal cortex (lateral) and left medial nodes.

Within-network connectivity was calculated by averaging all ROI-to-ROI connections of a given network. This was done in a stepwise manner. First, pairwise correlations between time series of regions within the two hemispheres and between hemispheres were averaged. In a second step an average was calculated using these previously computed average connectivity values (average right, average left, average between-hemisphere values). For the between-network connectivity, time series of DMN regions were correlated with time series of SN-regions of the SN; followed by averaging of these pairwise correlations using the same stepwise approach as for the within-network connectivity (i.e. hemisphere-specific averages).

2.6. Statistical analysis

Linear mixed effects (LME) analysis (lme4 package (v. 1.1–18-1) in R (v. 3.5.2); Bates et al., 2014) was performed to assess level and longitudinal change of the within-DMN, within-SN and between-DMN-SN connectivity. As fixed effects we included *time* (baseline, 1-y follow-up, 2-y follow-up, 4-y follow-up, 7-y follow-up), *predtrauma* (individuals with trauma exposure = 1, indivdiuals without trauma exposure = 0) and *predPTSD* (individuals with PTSD symptoms = 1, indivdiuals without PTSD symptoms = 0), as well as their interaction term, in our models. Random effects were subject-specific intercepts and slopes. Additionally, *age at baseline*, *gender* (female = 0, male = 1) and *education* were included as covariates since previous research has shown that age (Malagurski et al., 2020), gender (Tomasi and Volkow, 2012), and education (Chan et al., 2018) are related to the topological organization and functional connectivity of the brain. The dependent

variables were within-DMN connectivity, within-SN connectivity, and between-DMN-SN connectivity.

The best-fitting LME was determined via a manual stepwise forward selection procedure. First the random effects structure was determined for which a base model (including only the covariates and a random intercept by subject) was compared to a more complex model including the effect of time, and subsequently to a model including random slopes for participants. Improvements of model fit were assessed using likelihood ratio tests, performed on models fit using maximum likelihood estimation and restricted maximum likelihood estimation. More specifically, models were compared using the difference $\chi 2$ test, the Bayesian Information (BIS) and the Akaike Information Criterion (AIC). In model comparison, smaller values of BIC ad AIC indicated a better model fit. The significance threshold for the $\chi 2$ test was set to $p < 0.05$.

A similar model fitting procedure (i.e. model comparison) was used to determine if the two predictors – predtrauma and predPTSD – contributed to an improved model fit.

Separate models were fitted for each type of network connectivity (within-DMN, within-SN and between-DMN-SN). In the first step, to describe the connectivity metrics and their trajectories and assess the influence of trauma experience, we ran models that included the full sample. In the second step, to determine if the presence of PTSD symptoms affects resting-state connectivity, we ran additional models that were limited to individuals with trauma exposure. An adjustment for multiple comparisons using the Bonferroni correction was performed. Effect sizes were calculated using the R package *effectsize* by converting F statistics to partial Eta squared (η_p^2) (Friedman, 1982).

As the trauma inventory specifically assessed the PTSD symptom expression within the last months and was administered at the 4-year follow-up, an additional multivariate analysis of variance (MANOVA) only using the rs-FC data of the 4-year follow-up (e.g., within-DMN, within-SN and between DMN-SN) as dependent variables, was run for individuals who reported trauma exposure as to examine differences in rs-FC at the 4-year follow-up between individuals who reported PTSD symptoms and individuals without symptoms.

3. Results

3.1. Within-DMN connectivity

For within-DMN connectivity, the LME model that assumes no change across measurement occasions had the best fit (Supplementary Table 1). The baseline model showed a significant effect of gender, qualified by lower within-DMN connectivity in male as compared to female participants ($b = -0.0170$, $SE = 0.0062$, 95% CI [−0.0290, −0.0052], $p = 0.0062$). There was no evidence for effects of age or education on within-DMN connectivity. In the next modeling step, where trauma exposure was added as a predictor to the model, we found no differences between individuals with and individuals without trauma exposure ($p = 0.6384$). The effect of gender on within-DMN connectivity, survived the Bonferroni correction (alpha = 0.05/3).

Lastly, the LME model restricted to those individuals who had

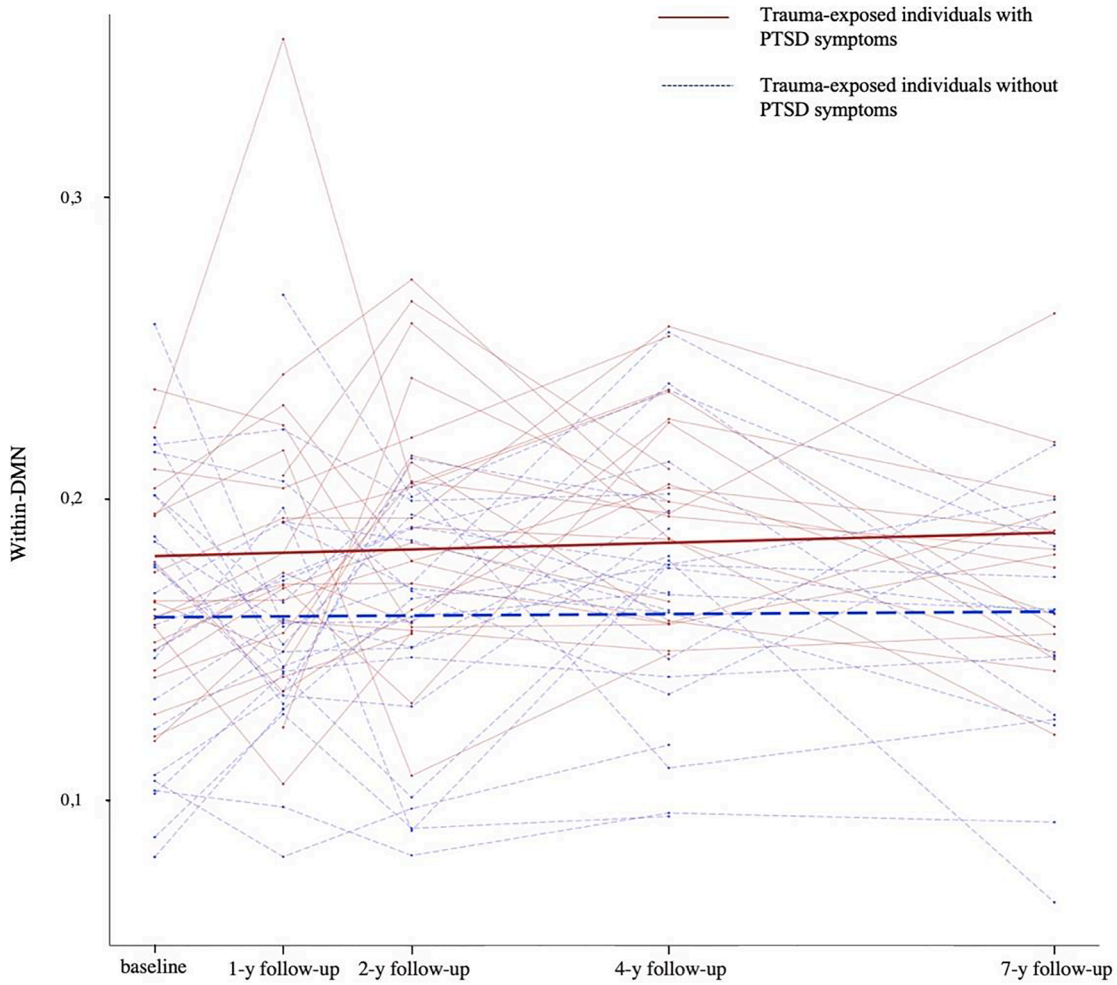

Fig. 1. Spaghetti plot of the raw data of the within default mode network connectivity across the five time points. Within-DMN = average connectivity within the default mode network.

trauma exposure and including PTSD symptoms as additional predictor showed that within-DMN connectivity was lower for individuals with PTSD symptoms as compared to those not reporting symptoms ($b = -0.0215$, $SE = 0.0091$, 95% CI [−0.0387, −0.0043], $p = 0.0222$) with an effect size of $\eta_p^2 = 0.11$, as displayed in Fig. 1. The effect of individuals with PTSD symptoms on within-DMN connectivity did not survive the Bonferroni correction (alpha = 0.05/3). There was no evidence for effects of age, gender or education on within-DMN connectivity. Model estimates are listed in Table 2 and 3.

3.2. Within-SN connectivity

For within-SN connectivity, the LME model that assumes no change across measurement occasions yet again had the best fit (Supplementary Table 2). There was no evidence for effects of age, gender or education on within-SN connectivity. In the next modeling step, individuals with trauma exposure showed a trend for greater within-SN connectivity ($b = 0.0175$, $SE = 0.0103$, 95% CI [−0.0173, 0.0229], $p = 0.0909$), with an effect size of $\eta_p^2 = 0.03$.

Lastly, when running an LME model restricted to those individuals who had trauma exposure and including PTSD symptoms as additional predictor, we found no evidence for effects of age, gender or education on within-SN connectivity. Also, the within-SN connectivity was not lower for individuals with PTSD symptoms ($p = 0.5548$). Model estimates are listed in Table 2 and 3.

3.3. Between-network connectivity

For between-network connectivity, the LME model with time as a fixed effect (assuming similar change for all subjects across measurement occasions) had the best fit ($b = 0.0043$, $SE = 0.0011$, 95% CI [0.0049, 0.0082], $p < 0.001$), with an effect size of $\eta_p^2 = 0.14$. Furthermore, age ($b = 0.0025$, $SE = 0.0010$, 95% CI [0.0006, 0.0043], $p = 0.0107$) and gender ($b = 0.0436$, $SE = 0.0093$, 95% CI [0.0256, 0.0612], $p < 0.001$) had a significant impact on between-DMN-SN connectivity, qualified by lower between-network connectivity in female as compared to male participants and a gradual increase of between-DMN-SN by age. In the next modeling step, there were no significant differences in the between-DMN-SN connectivity between individuals with or without trauma exposure ($p = 0.9844$). The effect of age and gender on between-network connectivity survived the Bonferroni correction (alpha = 0.05/3).

Lastly, in the LME model restricted to those individuals who had trauma exposure and including PTSD symptoms as additional predictor, male participants had a higher between-DMN-SN connectivity ($b = 0.0491$, $SE = 0.0152$, 95% CI [0.0201, 0.0787], $p = 0.0023$), whereas age and gender had no effect on between-DMN-SN connectivity. The between-DMN-SN connectivity was not greater for individuals with PTSD symptoms ($p = 0.5548$) or individuals with trauma exposure ($p = 0.9844$). The effect of gender on between-network connectivity survived the Bonferroni correction (alpha = 0.05/3). Model estimates are listed in Table 2 and 3.

3.4. Post-traumatic stress symptoms and functional conncectivity at 4-year follow-up

Comparing individuals with trauma exposure and no PTSD symptoms with individuals with PTSD symptoms on the three functional connectivity metrics at 4-year follow-up narrowly missed significance ($F(1, 3) = 4.458$, $p = 0.058$; Wilk's $\Lambda = 0.838$, $\eta_p^2 = 0.092$). In line with the predictions of the LME models reported above, post-hoc tests reveal the following picture: In comparison to the individuals without PTSD symptoms, individuals with PTSD symptoms showed significantly lower within-DMN connectivity at 4-y follow-up (PTSD symptoms: $M = 0.1723$, $SD = 0.0424$; no PTSD symptoms: $M = 0.1961$ $SD = 0.0334$; $p = 0.041$), but no differences with regard to within-SN connectivity (PTSD symptoms: $M = 0.2191$, $SD = 0.0722$; no PTSD symptoms: $M = 0.2124$ $SD = 0.0607$, $p = 0.550$) and between-network connectivity (PTSD symptoms: $M = 0.0398$, $SD = 0.0725$; no PTSD symptoms: $M = 0.0217$ $SD = 0.0758$, $p = 0.412$). See Table 4 for the MANOVA results.

4. Discussion

Using a non-clinical older adult sample (aged > 65 years) the present study examined differences in within-DMN, within-SN and between-DMN-SN rs-FC in trauma-exposed individuals with and without PTSD symptoms as well as non-trauma exposed individuals. We found that within-DMN connectivity was insensitive to trauma exposure, but lower in individuals who reported PTSD symptoms compared to individuals without symptoms. Within-SN connectivity (trend level), on the other hand, was higher in trauma-exposed individuals – independent of whether they reported PTSD symptoms or not – compared to non-trauma exposed individuals.

Although previous studies have reported lower within-DMN connectivity in trauma-exposed individuals, from those studies we cannot conclude whether this stems from the mere exposure to traumatic events or is related to PTSD symptom manifestation (Bluhm et al., 2009; DiGangi et al., 2016; Sheynin et al., 2020). Our data suggest that lower within-DMN rs-FC is associated with PTSD symptoms manifestation and not with trauma exposure per se (Kunimatsu et al., 2020; Sheynin et al., 2020). Assuming that, in previous studies, the trauma exposure groups had a higher symptom load (e.g., combat-exposed veterans), one could hypothesize that this causes the observed difference between the trauma exposure and non-trauma exposed groups (DiGangi et al., 2016). When symptom load is low, as in our dataset comprising healthy older adults, the symptom-related effect may be masked when only looking at the trauma exposure group as a whole. Our result is also well in line with the fact that DMN activity has been linked to self-referential and other introspective processing (Buckner and DiNicola, 2019) possibly pointing towards an abbarent coping mechanism in individuals with PTSD

Table 2
Linear mixed effect models of the within- and between-network connectivity for the entire sample $N = 110$.

Network	Predictors	Estimates	SE	η_p^2	CI	p
DMN	Age	−0.0009	0.0006	0.02	[-0.0022, 0.0003]	0.1486
	Education	0.0013	0.0035	0.0001	[-0.0055, 0.0081]	0.7144
	Gender	−0.0170	0.0062	0.07	[-0.0290, −0.0052]	0. 0062*
SN	Age	−0.0019	0.0011	0.03	[-0.0039, 0.0002]	0.0885
	Education	−0.0026	0.0060	0.0002	[-0.0141, 0.0089]	0.6621
	Gender	0.0030	0.0104	0.0001	[-0.0170, 0.0230]	0.7849
	predtrauma	0.0175	0.0103	0.03	[-0.0173, 0.0229]	0.0909
BN	Age	0.0025	0.0010	0.06	[0.0006, 0.0043]	0.0107*
	Education	0.0002	0.0053	0.0000	[-0.0103, 0.0103]	0.9971
	Gender	0.0436	0.0093	0.18	[0.0256, 0.0612]	< 0.001**
	Time	0.0043	0.0011	0.14	[0.0049, 0.0082]	< 0.001**

Note. Only models with the best model fit indices are shown; DMN = default mode network, SN = salience network, BN = between-network connectivity DMN-SN, predtrauma = individuals with trauma exposure; η_p^2 = partial eta squared;*$p < 0.05$; **$p < 0.001$.

Table 3
Linear mixed effect models of the within- and between-network connectivity for individuals with trauma exposure $n = 50$.

Network	Predictors	Estimates	SE	η_p^2	CI	p
DMN	Age	−0.0008	0.0009	0.0002	[-0.0026, 0.0010]	0.3914
	Education	0.0031	0.0055	0.0007	[-0.0074, 0.0135]	0.5774
	Gender	−0.0074	0.0094	0.01	[-0.0254, 0.0104]	0.4356
	predPTSD	−0.0215	0.0091	0.11	[-0.0387, −0.0043]	0.0222*
SN	Age	−0.0023	0.0017	0.04	[-0.0056, 0.0010]	0.1914
	Education	0.0013	0.0106	0.0001	[-0.0174, 0.021]	0.8942
	Gender	0.0178	0.0170	0.02	[-0.0153, 0.0497]	0.3004
BN	Age	0.0012	0.0015	0.01	[-0.0018, 0.0041]	0.4175
	Education	−0.0094	0.0089	0.02	[-0.0264, 0.0078]	0.2976
	Gender	0.0491	0.0152	0.19	[0.0201, 0.0787]	0.0023*
	Time	0.0059	0.0014	0.10	[0.0043, 0.0119]	< 0.001**

Note. Only the models with the best fit are shown; DMN = default mode network, SN = salience network, BN = between-network connectivity DMN-SN, predPTDS = individuals with post-traumatic stress disorder symptoms; η_p^2 = partial eta squared;*$p < 0.05$; **$p < 0.001$.

Table 4
Results of a One-Way MANOVA at 4-year follow up for individuals with trauma exposure.

Network	predPTSD $n = 24$		No predPTSD $n = 22$				
	M	SD	M	SD	F	p	Eta^2
DMN	0.1723	0.0424	0.1961	0.0334	4.458	0.041*	0.092
SN	0.2191	0.0722	0.2124	0.0607	0.363	0.550	0.008
BN	0.0398	0.0725	0.0217	0.0758	0.687	0.412	0.015

Note. *p < 0.05; **p < 0.001; DMN = default mode network, SN = salience network, BN = between-network connectivity DMN-SN, predPTSD = individuals with post-traumatic stress disorder symptoms.

symptoms. Whether the manifestation of PTSD symptoms potentiates the aging effect within individuals over time (causing steeper within-subject slopes) can, however, not be verified in the present study, since our within-DMN models favored stability of rs-FC over change. This stability of rs-FC fits well with the conclusions of a recent review article, in which Jockwitz and collegues conclude that age and aging effects in within-network rs-FC are mostly evident when comparing different age-cohorts while the findings are much less clear in age homogeneous samples of older adults, particularly for within-DMN connectivity (Jockwitz & Caspers, 2021).

With respect to the salience network, we observed greater within-SN connectivity in trauma-exposed compared to non-trauma exposed individuals (trend level) while there was no difference between individuals with and without PTSD symptoms. This may suggest that trauma exposure itself can be associated with functional connectivity changes also in non-clinical older adult poulations. Greater within-SN connectivity in trauma exposed individuals is thought to represent a hyperactivation in response to relevant stimuli but also in a more general way – as an unbalanced attention capturing resulting from an distorted detecting and filtering mechanism of incoming information (Menon, 2011). Several authors even propose that tackeling within-SN rs-FC may be the working mechanism of action for evidence-based trauma therapy. In more detail, a recent review using MRI to predict cognitive-behavioral therapy outcome and prolonged exposure (guided repeated imaginal and in vivo exposure exercises) (Peterson et al., 2019) showed that a positive treatment response was associated with an improvement in regulating the amygdala by means of the SN (Szeszko & Yehuda, 2019). So far, however, previous research has reported greater within-SN merely in young to middle-aged clinical samples (Sheynin et al., 2020; Stark et al., 2015). Considering the observed trend of increased within-SN rs-FC in trauma-exposed individuals in our non-clinical sample together with the fact that symptoms are often on a subthreshold level in older adults (Pietrzak et al., 2012), future studies should aim to examine bigger non-clinical cohorts as to merit further definite conclusions if within-SN rs-FC is affected by trauma exposure and, thus, deserves further attention in subclinical treatment. Furthermore, also the type of exposure to a potentially traumatic event (e.g., man-made, natural disaster) not included within the present analysis might relate to differential neural correlates and hence could have influenced the trend level finding of the present analysis. As for the within-DMN connectivity, our data do not support significant change of within-SN rs-FC over time. However, the effect of age on within-SN connectivity (i.e., lower connectivity in higher age) within the studied timeframe (e.g., seven years), although not significant, is consistent with previous work and our hypotheses. Hence, in contrast to the DMN, we see opposing effects of aging and trauma exposure. In order to answer the question of how the observed within-SN hyperconnectivity in individuals with a trauma history and the previously reported age-related decline in within-SN rs-FC might co-exist or interact needs further research for clarification.

With respect to between-network connectivity, the present findings do not support an effect of trauma exposure or PTSD symptom manifestation on rs-FC in our subclinical sample of older adults. Our models solely supported a gradual increase of between-DMN-SN connectivity across time in the full sample, which is consistent with previous rs-FC findings in healthy aging (Chan et al., 2014; Geerligs et al., 2015; Malagurski et al., 2020; Song et al, 2014; Zonneveld et al., 2019). However, trauma exposure or symptom manifestation were not associated with between-network connectivity changes across time. As suggested in a recent review on MRI findings in PTSD, between-network connectivity may change as a function of the time period during which the trauma exposure occurred (Kunimatsu et al., 2020). More precisely, it has been shown that lower between-network connectivity is associated with early-life trauma (Bluhm et al., 2009), whereas greater between-network connectivity is observed in veterans with trauma exposure in later life (Sripada et al., 2012). Unfortunately, the design and sample size of the present study does not allow to investigate if the time period of trauma exposure may be a moderator. Hence, it is possible that in our study opposing effects diminished a potential influence of trauma exposure or PTSD symptoms on between-DMN-SN rs-FC. Future investigations are encouraged to improve our knowledge of how the communication between networks is affected by trauma exposure and PTSD symptom manifestation as to better understand the role of the time period during which trauma exposure occurred.

Fail to the grasp of complexity, besides the strong value of the incorporated three group differentiation and oftentimes previously

underrepresented older age group in the present study some limitations need to be considered when interpreting our findings. First, the sample size was relatively small. Future studies collecting and retaining larger cohorts with and without PTSD symptoms following trauma-exposure, should be considered. Despite the comparably small sample size, 45.5% of the individuals in our sample reported to having been exposed to at least one potentially traumatic event. This is slightly lower than in a previous population based study (Glaesmer et al., 2010) who reported rates of 59.7% – 64.3% of exposure to potentially traumatic events in their older adult sample (aged > 60 years). However, given the fact that, historically, the Swiss population was less affected by World War II related trauma exposure as compared to the German older adult sample, the lower exposure rates in the present sample seems reasonable (Glaesmer et al., 2010). Second, the present sample was composed of non-clinical older adults, hence no definite conclusions can be drawn with regard to rs-FC and clinical diagnostic status. It should be considered that frequency and intensity of reported symptoms was low in the present sample. Although 50% of the trauma-exposed individuals reported at least one symptom that is linked to PTSD, only two participants would meet common diagnostic criteria for PTSD (Siegrist & Maercker, 2010). Previous studies have observed prevalence rates of 0.7% for PTSD and 4.2% of subsyndromal PTSD in older age (65 to 96 years old) (Maercker et al., 2008), which is in line with our data. Third, the trauma exposure and post-traumatic stress measures were only assessed at the 4-year follow-up and participants were asked to indicate symptom manifestation within the last 4 weeks. One might argue, that this does not permit to use PTSD symptoms in our longitudinal dataframe. However, since the three most prominent forms of PTSD in older age are 1) exposure to a traumatic event within the last two years, 2) chronic PTSD following early life adversity and 3) delayed onset PTSD (Maercker, 2021), which are most probable associated with symptom manifestation over a longer time period, we are confident that this does not significantly affect our analyses. Furthermore, we performed an additional analysis specific for the 4-year follow-up measurement occasion, which gave comparable results and, thus, supports the above given interpretation. Nevertheless, future studies might benefit from additionally including the spectic time-point of exposure to the traumatic event and its temporal distance to the longitudinal measurements. This might provide the field with more insight on the effect of timing of the exposure to the potential traumatic event. We would further like to mention that next to investigations using rs-fMRI the field has recently also studied rs-FC in individuals with PTSD using EEG, which might complement several methodological difficulties associated with rs-fMRI (Schlumpf et al., 2021; Heinrich et al., 2014; Mutschler et al., 2014). Future investigation might therefore benefit from using a multimodal approach in studying rs-FC. Moreover, future investigations could also benefit by including markers of cognition when examining SN and/or SMN connectivity in older aging participants as there is accumulating evidence for age-related decrease in interhermispheric resting-state functional connectivity and cognition (Hausman et al., 2020; Zhao et al., 2020). Furthermore, the effect of PTSD symptom expression and in association with the exposure to potentially traumatic events were only observed on a trend level. However, eta squared as a measure of effect size revealed a medium effect size of PTSD symptoms on within-DMN ($\eta_p^2 = 0.11$) and a small effect for trauma exposure on within-SN($\eta_p^2 = 0.03$) (Cohen, 1988).

To summarize, in this study we, for the first time, investigated the differential effects of trauma exposure and PTSD symptom manifestation on rs-FC and its change within individuals by using a three group differentiation (e.g., non-trauma exposed individuals, trauma exposed individuals and individuals exhibiting PTSD symptoms) in a non-clinical sample of older adults. Observed trends fit well with the previous observations in clinical samples of individuals with PTSD showing disturbances of self-perception and consciousness associates with altered within-DMN rs-FC and hence help to further our understanding regarding the neural basis of PTSD. Moreover, present findings may help to underscore the importance of studying the magnitude of a traumatic event in non-clinical populations given the observed trend for altered within-SN connectivity in the present sample as to understand potential implication of trauma exposure without significant symptom manifestation over the life span and older age stages. Altogether, present results suggest that alterations in within-DMN and within-SN rs-FC can also be observed in non-treatment seeking older adult populations following trauma exposure and in association with PTSD symptoms.

5. Ethics statement

This study involving human participants was reviewed and approved by the Ethics Committee of the Canton of Zurich. The participants provided their written informed consent to participate in this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103052.

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