THE COMPLEX BIOPSYCHOSOCIAL INTERACTIONS THAT CREATE STRESS RESILIENCE

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THE COMPLEX BIOPSYCHOSOCIAL INTERACTIONS THAT CREATE STRESS RESILIENCE

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EDITORIAL
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Editorial: The Complex Biopsychosocial Interactions That Create Stress Resilience

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Editorial on the Research Topic

The Complex Biopsychosocial Interactions That Create Stress Resilience

Stress is present in our daily surrounding. Although it is essential for survival and functioning, it may become pathological when coping strategies are dysfunctional. While some people are vulnerable, others are more resistant to stressors. Although individual variability in stress resilience has been well-characterized, its underlying mechanisms remain elusive. Resilience is a dynamic process related to the individual's capacity to adaptively cope with adversity, trauma, threats or significant stressors. While a small proportion of individuals succumb to traumatic events or chronic stress and develop stress-related psychiatric disorders, most people are not severely affected and some may even flourish in adverse or stressful circumstances. Biologic, psychological and social factors interact with each other creating a physiologic and behavioral repertoire, which may enable individuals to thrive in face of adversity.

At present, stress resilience and coping strategies are important tools for the treatment of psychiatric diseases. In this Research Topic entitled "The Complex Biopsychosocial Interactions that Create stress Resilience" we have brought together the most recent research findings in resilience to stress. Original and review papers on pre-clinical models and human populations present different aspects of what is collectively known as resilience. The volume is organized in four themes: Resilience after stressful experiences, Social effects on resilience, Positive effects on stress resilience and Effects of resilience in professional caregivers.

The review by Matheson et al. presents concepts related to psychosocial factors of resilience and the importance of coping strategy, social support and spirituality in dealing with different scenarios of social adversity, such as psychological abuse in intimate relationships, political, ethnic and religious refugees, and indigenous peoples. Traumatic events early in life may represent a risk factor for the development of emotional psychiatric disorders. Evaluating 170 community-dwelling adults, Seok et al. investigated the interaction between early trauma (e.g., abuse and neglect during childhood) and recent stressful events on depression, anxiety and anger symptoms at adulthood. Although recent stressors increase anxiety, the interaction of early life trauma and recent stressors potentiate depression and anger scores. To investigate the impact of early life adversity on an elder population, Thoma et al. assessed victims of a wide range of childhood adversity (risk group) and an age-matched control group for their resilience resources and self-esteem. They used a network analysis of specific resilience factors and showed that both the risk and control groups

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demonstrated positive resilience resource interrelations. This may be useful for the development of potential clinical intervention targets in adult or elderly survivors of early life adversity. Besides early life adversity, natural disasters are likely to result in emotional disorders, including depression and posttraumatic stress disorder (PTSD). The study by Rossi et al. with university students who survived an earthquake in L'Aquila, Italy, showed that exposure, material loss or psychological suffering associated with the event did not affect the students in any major way. This, however, was reported in individuals with a high perception of self.

Social animals and humans show better recovery from stressful experiences when in groups. Two studies in this Research Topic have focussed on social aspects, cognition and stress coping. Souza-Talarico et al. investigated the role of social support in a population-based cohort of older adults, showing that high levels of family and community support increased cognitive performance. Emotional components of social support (e.g., loving and empathy) were critical in the relationship between social interactions and cognitive health (Souza-Talarico et al.). The impact of social relationships on general health can be tested in pre-clinical studies using social isolation or individual housing. Using this paradigm in an animal model of breast cancer, Berry et al. demonstrated that social isolation increased corticosterone levels, decreased active coping behavior and gene expression of neuropeptide Y, and other molecular elements related to metabolism. In addition, social isolation increased the vulnerability of female mice to maladaptive behaviors, accelerated the development of breast cancer and impaired the regulation of resilience factors.

Besides social buffering, other factors also positively contribute to resilience. Roversi et al. used a tactile stimulation approach early in life in a genetic model of anxiety and depression to explore the effects of beneficial stimuli. Serotonin transporter (5-HTT) heterozygous knockout (5-HTT+/-) rats serve as a model of the human short polymorphism of the 5-HTT, known to be more vulnerable to stress (Houwing et al.). Mimicking maternal licking and grooming, tactile stimulation administered in 5-HTT+/- offspring was shown to improve social and affective behaviors and alter molecular parameters related to glucocorticoid, GABA and glutamate functioning. Ketamine, an NMDA receptor antagonist, modulates the glutamatergic system, and is currently being used in several stress-related and alcohol use disorders. The review by Strong and Kabbaj provides evidence of the effectiveness of ketamine treatment on neuroplasticity induced by chronic alcohol use. In a narrative review, Arida and Teixeira-Machado polled 18 studies to summarize the benefits of aerobic fitness to brain resilience from early stages of life to the elderly. Exercise was found to enhance cognitive capacity of the offspring by increasing postnatal neurogenesis and neuronal growth. During adulthood and aging, aerobic exercise protects individuals from cognitive decline and depression by reducing neuroinflammation and increasing neuroplasticity, angiogenesis, and brain vasculature. Brain derived neurotrophic factor has been suggested to mediate those positive effects by counterbalancing the negative stress consequences.

Providing health care may come with a risk for professional caregivers, which are often faced with stress as part of their job. Dealing with psychiatric patients exposed to trauma may sometimes personally expose healthcare workers to harm (e.g., verbal and physical aggression). This, along with the heavy workload and unpredictable schedules, may lead to stress-related disorders. Indeed, health care professionals are more likely to develop burnout syndrome than the general population. In a study with Chinese nurses, Song et al. explored the mediating role of sleep on perceived stress and job burnout. They report that stress has a direct impact on burnout leading to poor quality of sleep. The authors propose that interventions and strategies that improve sleep quality and stress coping may improve health in general. Stress resilience in health care professionals may be a buffer for stress-related problems and increase job satisfaction. Bürgin et al. investigated the sense of coherence (SoC), self-efficacy, self-care and measured stress markers in youth residential caregivers. SoC and self-care were both associated with lower cortisol: DHEA (dehydroepiandrosterone) ratio implying that youth residential institutions may want to provide programs that enhance SoC and self-care practices to improve the health of caregivers. The results presented in this Research Topic demonstrate a crucial role for biopsychosocial interactions in the resilience for stress and proposes several indicators to create stress resilience.

AUTHOR CONTRIBUTIONS

DS, JS-T, CH, and JO contributed to the writing and editing of the text. All authors read and approved the final version of the manuscript.

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ResilienCity: Resilience and Psychotic-Like Experiences 10 Years After L'Aquila Earthquake

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An earthquake hit the city of L'Aquila in central Italy in 2009, leaving the city completely destroyed and 309 casualties. Unexpectedly, lower rates of psychotic experiences in persons affected by the earthquake compared to non-affected persons were found 10 months after the earthquake. The very long-term impact of a natural disaster on the prevalence of psychotic experiences deserves more in-depth detailing. The Authors examined resilience and psychotic experiences in a university student sample of 494. No effect of direct exposure to the earthquake (odds ratio = 0.64, 95%CI [0.37, 1.11]), material damages (odds ratio = 0.86, 95%CI [0.60, 1.23]), psychological suffering (odds ratio = 1.06, 95% CI [0.83, 1.36]), or global impact severity (odds ratio = 0.92, 95%CI [0.76, 1.12]) on psychotic experiences was detected. Resilience levels did not differ between affected and non-affected persons. Resilience showed a strong protective effect on psychotic experiences (odds ratio=0.38, 95% CI [0.28, 0.51]. The protective effect of the RSA factor "Perception of Self" was significantly stronger in individuals affected by the earthquake compared to non-affected subjects. Being affected by an earthquake is not a risk factor for psychotic experiences in a university student sample, as no direct effect of the earthquake was detected after 10 years after the event. Resilience is confirmed as a strong protective factor for psychotic experiences irrespectively of large collective traumatic events. Extension of these results to a general population sample could provide interesting insights into recovery from natural disasters.

Keywords: psychotic-like experiences, trauma, adverse life experiences, natural disaster, earthquake

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INTRODUCTION

An earthquake (EQ) of 6.3 magnitude hit the city of L'Aquila in central Italy on April 6th 2009, leaving the city completely destroyed. Three hundred and nine lost their lives and thousands were injured. After the earthquake, the entire population of the city (>60.000) was displaced either in nearby touristic areas or in tent camps within the city. Only a fraction of the population

could return to their homes in the short-term, while the rest of the population had to wait several years for the reconstruction to take place. As of today, reconstruction still struggles to take place, with at least 5,000 people who are still living in transitioning housing, and the productive capacity and supporting infrastructure is still left behind, in favor of a slow, building-by-building reconstruction. The slow reconstruction procedures, more than the earthquake itself, have profoundly affected the social context of the town and its dwellers (1).

Traumatic events represent a risk factor for a plethora of psychological and psychiatric disorders, including psychotic-like experiences (PLEs). However, the equivalence of different types of trauma, such as natural disasters or interpersonal traumatic events, as risk factors for psychotic symptoms is still debated (2).

PLEs are considered a major risk factor for subsequent transition to psychotic disorders (3) as they share a number of risk factors with major psychotic disorders, including neurocognitive abnormalities (4) and traumatic events (5).

The putative mechanisms through which trauma sensitizes vulnerable individuals within the psychosis continuum include cognitive mechanisms (6), as well as stress-induced neurobiological and HPA-axis modifications (7). Interpersonal stressful life events have been repeatedly associated with PLEs (5, 8, 9). On the other hand, natural disasters affect the incidence of several mental disorders (10); however, their relevance as risk factors for PLEs is controversial. Natural disasters showed a weak effect on PLEs rate compared to interpersonal traumatic events in a large international study (2). Local studies have found opposite results (11, 12). The very long-term impact of a natural disaster on the prevalence of PLE has not been addressed so far.

We reported on the prevalence of PLEs in a group of adolescents 10 months after the 2009 EQ. Unexpectedly, lower rates of PLEs in persons affected by the EQ, compared to non-affected persons were found (13), with marginal associations between post-traumatic symptoms and PLEs (14).

A number of putative protective factors may have contributed to the evidence of lower PLEs rates in individuals affected by the EQ, including resilience. Resilience has been shown to play a strong protective effect along the entire psychosis spectrum, from PLEs (15, 16) to schizophrenia (17–19). Regarding the 2009 EQ, resilience could have buffered or moderated the stressful effects, resulting in lower levels of PLEs regardless emotional distress associated with post-traumatic symptoms.

As we previously observed, the population in L'Aquila could have expressed unexpected levels of resiliency (20, 21). Therefore, if these levels of resilience were preserved in the population, PLEs rates should not differ between affected and non-affected individuals 10 years after the event. Our goal is exploring any difference in resilience levels between affected and non-affected by the 2009 EQ. Furthermore, we aim at measuring the effects of EQ 10 years after the event on rates of PLEs in a sample of University students using an on-line survey. Our hypothesis, based on previous reports on levels of resilience in the population of L'Aquila, is that the impact of the earthquake on PLEs is negligible.

METHODS AND MATERIALS

Sample

Participants were university students at the University of L'Aquila. Data were collected over the period of June 2018 until April 2019 using a research website designed for this purpose (LimeSurvey®). Participants were recruited *via* advertisements on various social networks connected to the University. Recruitment was automatically closed when five hundred persons had participated. In order to detect random answering, six verification items were included as a measure of validity throughout the survey. Two thousand six hundred and sixty-seven volunteers visited the survey site, 500 gave consent, correctly answered all the attention checks and completed the questionnaire. Participants provided written consent for data collection and analysis. Ethical approval was obtained from the local Law and Ethics Committee and the local research ethics. The research adheres to the tenets of the Declaration of Helsinki.

Measures

Prodromal Questionnaire-16, Italian Version

The presence of PLEs was assessed using the Italian version of the Prodromal Questionnaire-16 (iPQ-16) (22). iPQ-16 is a 16-items self-report instrument that explores the presence/absence of 16 PLEs, including perceptual aberrations/hallucinations, unusual thought content/delusions, and two negative symptoms, and their associated psychological distress score on a four-point likert scale ranging from 0 to 48. Although the iPQ-16 was originally designed as a screening tool for individuals at Ultra-High Risk in help-seeking populations, several studies have used this instrument in non-help-seeking samples as a measure of PLEs (15, 23–25). We used the distress scale as recommended by Savill et al., (26) for non-help-seeking populations, using a cut-off of ≥11 as recommended by Pelizza et al. (27) according to the Italian field test. In this data, the average interitem correlation was 0.17 and Cronbach's α 0.85.

Resilience

Resilience was measured using the Resilience Scale for Adults, Italian version (28). The RSA is a 33-item scale evaluating six first order factors (Perception if Self, Planned Future, Social Competence, Structured Style, Family Cohesion and Social resources) and two second order dimensions (Personal and Contextual Resilience). RSA is a reliable (Cronbach's α from.67 to.81) and stable (test-retest, Pearson r from.73 to.80) instrument (29). RSA has a semantic differential format on a 1 to 7 likert scale with higher scores indicating stronger resilience resources.

Earthquake Impact

The earthquake impact was primarily explored with a single question "where were you in on the day of the earthquake?",

considering affected only those individuals that reported being in L'Aquila and surroundings on the day of the disaster. Furthermore, the entity of material damages and subjective psychological suffering due to the earthquake were assessed by two single item questions on a four-point likert scale phrased as follows: "did the earthquake cause any material loss?" and "did the earthquake cause you any psychological suffering?" with 0 = "not at all" and 4 = "extreme loss/suffering". Due to the high number of minor shocks that preceded the main destructive one during the previous days, many citizens had already left the city when the earthquake hit L'Aquila. For this reason, material damages or psychological sufferings may have occurred independently from actually being in L'Aquila at the time of the earthquake, for example regarding material goods or significant others endangered by the earthquake, causing concern indirectly. Therefore, an impact-severity variable was computed as the sum of the scores of material damages and psychological suffering and set to zero for non-affected subjects in subsequent analysis, in order to separate the direct from the indirect traumatic experiences.

Potential Confounders

Potential confounders included in the survey were age, gender, family income (coded as low, mid or high), alcohol or drug abuse (coded as "abuser" if reporting "often" and "very often" use of alcohol or drugs) and family history of any mental disorder.

Statistical Analysis

Socio-demographic characteristics, as well as mean iPQ-16 and RSA mean scores, were calculated for affected and non-affected participants. Differences between the two groups were examined using t-test or χ^2 as appropriate.

Firstly, we compared resilience levels between affected and non-affected participants using the Mann-Whitney test for two independent samples, in order to account for non-normality of distribution of RSA values. Secondly, the unadjusted and adjusted effects of EQ, material loss, and psychological suffering on PLE were estimated using bivariate logistic regression. Finally, the unadjusted and adjusted effects of RSA on PLEs were estimated in a second wave of bivariate logistic regressions, in the whole sample and separately for subjects affected and non-affected by the EQ. In order to test any difference in the effect of Resilience on PLEs between affected and non-affected individuals, an interaction term for each RSA factor x earthquake was tested.

Due to the constraints imposed on the on-line survey, there were no missing data. However, some subjects provided invalid answers to some open questions, that were treated as missing data.

RESULTS

Sample Characteristics

Table 1 presents the characteristics of the sample. Of the 500 respondents, 6 provided invalid information on EQ impact, and were excluded from subsequent analysis. Of the remaining 494 persons, 176 (35.63%) were directly affected by the 2009 Earthquake. Mean age was 25.5 (5.84); 25 (5%) persons reported drug or alcohol abuse; 143 (28.6%), 343 (68.6%) 14 (2.8%) persons reported respectively low, middle, and high income; 76 (15.20%) reported having a 1st degree relative suffering from a mental disorder. Affected and non-affected persons did not differ in terms of gender, age, drug or alcohol abuse, and income. A difference in rates of family history of mental disorder in 1st degree relatives was found. In our sample, iPQ-16 distress mean score was 5.02 (s.d. 5.22); 74 (14.8%) individuals scored above cut-off.

TABLE 1 | Characteristics of the sample.

Variable	Total Sample N (%)/Mean (SD)	Non-affected by EQ N (%)/Mean (SD)	Affected by EQ N(%)/Mean (SD)	Statistics (t or χ^2)
n	494	318 (64.37%)	176 (35.63%)	
Gender				n.s.
Female	352 (71.26%)	230 (72.33%)	122 (69.32%)	
Male	142 (28.74%)	88 (27.67%)	54 (30.68%)	
Age	25.52 (5.85)	25.47 (5.82)	25.61 (5.92)	n.s.
Alcohol/drug abuse	24 (4.86%)	18 (5.66%)	6 (3.41%)	n.s.
Income				n.s.
Low	143 (28.74%)	94 (29.56%)	48 (27.27%)	
Mid	343 (68.42%)	218 (68.55%)	120 (68.18%)	
High	14 (2.83%)	6 (1.89%)	8 (4.55%)	
Family history of mental illness	75 (15.18%)	60 (18.87%)	15 (8.52%)	$\chi^2_{(1)}$ = 9.41 (p= 0.002)
iPQ-16				n.s.
Mean distress score	5.01 (5.24)	5.20 (5.39)	4.66 (4.94)	
n≥11 distress score	73 (14.78%)	53 (16.67%)	20 (11.36%)	
Earthquake Impact				n.s.
Material damages	0.27 (0.77)	0.07 (0.4)	0.65 (1.1)	
Psychological suffering	0.74 (0.97)	0.44 (0.77)	1.31 (1.04)	
Global Impact Severity[§]	0.51 (0.72)	0.25 (0.46)	0.98 (0.86)	

EQ, earthquake; iPQ-16, Prodromal questionnaire, Italian version; [§]Global Impact severity is the sum of Material Loss and Psychological Suffering, in subsequent analysis it is set to 0 in non-affected persons.

RSA in Affected and Non-Affected Persons by EQ

Table 2 reports mean and SD for the six RSA factors and RSA total score in affected and non-affected persons by EQ, and in the total sample. The Mann-Whitney test revealed no differences in RSA factors or total score between affected and non-affected persons (all p values between 0.147 and 0.797).

Effects of EQ on PLE

Results from logistic regression are presented in **Table 3**. No significant association was found between the 2009 earthquake and PLE [OR=0.64, 95% CI (0.37, 1.110)] nor with severity of material damages or losses [OR= 0.86, 95%CI (0.60, 1.23)] or psychological suffering [OR= 1.06, 95%CI (0.83, 1.36)]. Global impact severity was not associated with PLE [0.92 (0.76, 1.12)].

After adjustment for age, gender, income, alcohol/drug abuse, and family history of mental disorder, the results did not substantially vary.

Effects of RSA on PLE

Results of bivariate logistic regressions of RSA factors and total score on PLE are shown in **Table 4**. Higher levels of all of the RSA factors were associated with lower prevalence PLE, with OR ranging from 0.47 [0.38, 0.59] for "Perception of Self" to 0.78 [0.64, 0.96] for "Structured Style", and an overall OR of 0.38 [0.28, 0.51] for the RSA total score. After adjustment for age, gender, income, alcohol/drug abuse, and family history of mental disorder, the results did not vary substantially. RSA showed a stronger protective effect in affected subjects compared with non-affected individuals, with OR ranging respectively from 0.28 [0.16, 0.47] vs 0.55 [0.43, 0.70] for "Perception of Self" to 0.73 [0.5, 1.1] vs 0.81 [0.64, 1.01] for "Structured Style" factor. The RSA total score was 0.26 [0.14, 0.47] in affected subjects compared to 0.43 [0.31, 0.61] in non-affected subjects. After adjusting for age, gender, income, alcohol/drug abuse, family history of mental disorder, results did not vary substantially. Interaction terms between RSA factors and earthquake revealed a significant interaction for "Perception of Self" only [OR=0.5 (0.28, 0.90)].

TABLE 2 | Resilience levels in affected and non-affected.

Variable	Total Sample	Non-affected by EQ	Affected by EQ
Perception of Self	4.68 (1.28)	4.66 (1.30)	4.75 (1.25)
Planned future	4.70 (1.51)	4.64 (1.50)	4.83 (1.55)
Social Competence	4.88 (1.23)	4.86 (1.25)	4.90 (1.21)
Family cohesion	4.92 (1.53)	4.92 (1.52)	4.91 (1.56)
Social resources	5.63 (1.19)	5.65 (1.15)	5.59 (1.26)
Structured Style	5.12 (1.22)	5.08 (1.23)	5.19 (1.21)
RSA Total	4.99 (0.93)	4.97 (0.93)	5.03 (0.94)

EQ, earthquake; RSA, Resilience Scale for Adults. Mann-Whitney p values ranging from 0.147 to 0.797.

TABLE 3 | Bivariate logistic regression estimates on psychotic-like experiences (PLEs) as dependent variable.

PLE	Unadjusted OR [95% CI]	Adjusted OR [95% CI][a]
Affected by EQ	0.64 [0.37, 1.11]	0.82 [0.46, 1.47]
Material Loss	0.86 [0.60, 1.23]	0.97 [0.67, 1.40]
Psychological Suffering	1.06 [0.83, 1.36]	1.17 [0.90, 1.54]
Global Impact Severity[§]	0.92 [0.76, 1.12]	1.01 [0.83, 1.24]

EQ, Earthquake. [a]Adjusted for age, gender, income, alcohol/drug abuse, family history of mental disorder. [§]Global Impact Severity is the sum of Material Loss and Psychological Suffering, set to 0 in non-affected persons.

DISCUSSION

Summary of Findings

Long term effects of natural disasters, such as the 2009 L'Aquila earthquake, on PLEs are mostly unknown. We unexpectedly found lower levels of PLEs in affected adolescents compared to non-affected ones right after the EQ (13). In this study, we explored the effects on PLEs 10 years after an earthquake in a University student sample. No effects of EQ, material loss or psychological suffering on the rates of PLE were found. Resilience was confirmed as a strong protective factor for PLEs, with higher scores on all RSA factors being associated with lower rates of PLEs, irrespective of a natural disaster. Indeed, resilience levels did not differ between affected and non-affected persons. However, the protective effect of resilience as a total score, and "perception of self" factor in particular, was substantially stronger in subjects affected by the earthquake.

Comparison With Previous Literature

To the best of our knowledge, this is one of the few reports investigating the very long-term effects of a natural disaster on PLE. Overall, only a limited and conflicting evidence on the impact of natural disasters on PLEs exists (6). Ayub and colleagues (11) reported increased rates of psychotic symptoms after the 2005 Kashmir earthquake, although the absence of a control group didn't allow them to estimate the effects of the EQ on PLE. In a national survey in Sri Lanka (12), an association between PLE and being affected by a tsunami, occurred 10 years before, was found. However, such association did not hold after controlling for conflict-related trauma. Moreover, no effect on PLEs was found in a 20 year follow-up study on PLEs in individuals affected by bushfires in Australia (30). Data from the World Mental Health survey confirmed a weak effect of natural disaster of unspecified type on PLEs, that did not hold after controlling for confounders (2).

In our sample, the prevalence of PLEs is considerably higher than the lifetime prevalence of around 5% reported in the literature (31). This could be due to the use of a self-report instrument that could have overestimated PLE prevalence compared to semi-structured interviews. Estimates of the prevalence of PLEs in population-based samples vary considerably, mostly depending on the type of instrument used (3, 31–33). The prevalence in our sample is similar to a 19.1% found in another study using the Prodromal Questionnaire in a

TABLE 4 | Bivariate logistic regression estimates of resilience on psychotic-like experiences (PLEs).

PLE	Total sample		Non-affected by EQ		Affected by EQ		Interaction term[a]
	Unadjusted OR [95% CI]	Adjusted OR [95% CI][a]	Unadjusted OR [95% CI]	Adjusted OR [95% CI][a]	Unadjusted OR [95% CI]	Adjusted OR [95% CI][a]	OR [95% CI]
Perception of Self	0.47 [0.38, 0.59]	0.46 [0.37, 0.59]	0.55 [0.43, 0.70]	0.54 [0.42, 0,70]	0.28 [0.16, 0.47]	0.28 [0.16, 0.5]	0.5 [0.28, 0.90]
Planned future	0.58 [0.49, 0.69]	0.59 [0.49, 0.71]	0.62 [0.51, 0.76]	0.62 [0.50, 0.77]	0.51 [0.36, 0.70]	0.51 [0.35, 0.74]	0.81[0.55, 1.20]
Social Competence	0.75 [0.61, 0.91]	0.72 [0.58, 0.90]	0.78 [0.62, 0.99]	0.75 [0.58, 0.97]	0.65 [0.44, 0.96]	0.67 [0.44, 1.01]	0.83 [0.53, 1.30]
Family cohesion	0.71 [0.61, 0.83]	0.75 [0.63, 0.89]	0.75 [0.62, 0.90]	0.79 [0.64, 0.96]	0.61 [0.46, 0.81]	0.63 [0.46, 0.87]	0.81 [0.58, 1,10]
Social resources	0.61 [0.50, 0.73]	0.59 [0.48, 0.72]	0.58 [0.46, 0.75]	0.56 [0.43, 0.73]	0.61 [0.45, 0.83]	0.60 [0.42, 0.86]	1.00 [0.70, 1.50]
Structured Style	0.78 [0.64, 0.96]	0.84 [0.68, 1.02]	0.81 [0.64, 1.01]	0.85 [0.66, 1.10]	0.73 [0.50, 1.1]	0.77 [0.52, 1.10]	0.91 [0.58, 1.40]
RSA Total Score	0.38 [0.28, 0.51]	0.38 [0.28, 0.53]	0.43 [0.31, 0.61]	0.43 [0.29, 0.62]	0.26 [0.14, 0.47]	0.27 [0.14, 0.52]	0.60 [0.30, 1.20]

EQ, Earthquake. Adjusted for age, gender, income, alcohol/drug abuse, family history of mental disorder. [a]Interaction term, EQ x RSA factors. RSA, Resilience Scale for Adults.

community sample (9). In this study, however, the number of endorsed items, rather than the distress score, was taken into account, contrary to what suggested by Savill and colleagues (26).

Meaning

Our findings represent the first report on PLEs at a such long time after a natural disaster. To the best of our knowledge, the interactions between resilience and PLEs in response to a natural disaster have not been addressed so far. Moreover, the generally accepted theory is that traumatic events, independently of their type, negatively affect PLE (6). Our current findings, if confirmed by larger and more rigorous epidemiological studies, could challenge this assumption, suggesting to reconsider the effect of natural disasters on PLEs rates in the light of individual or contextual resilience factors (34, 35).

Non-deterioration or even improvement in psychotic symptoms soon after being affected by a man-made disaster, including terror attacks, has been already proposed (36). Among the potential protective factors, resilience is of pivotal importance in contrasting the effects of traumatic events and in mitigating the impact of psychological symptoms (18, 37). Consistently, resilience levels did not differ between affected and non-affected individuals in our sample. The mean age in our sample is 25, which means that participants were, on the average, in their adolescence when affected by the earthquake. This is a critical aspect, because stressful life events have their major impact when occurring during adolescence. However, assuming that risk factors play their strongest disruptive effect during adolescence, it is reasonable to state that also protective factors could exert their maximum protection during the same period. Resilience has already been involved in mitigating the onset of PLEs (16). Our findings suggest that the 2009 EQ affected a resilient population that may have bounced back during the immediate aftermaths of the EQ, and that may have fully recovered, in terms of PLE rates, 10 years after. If the EQ produced immediate psychological symptoms, resilience could have promoted a quick subjective process of personal recovery in heavily traumatized individuals (38).

The exact protective mechanisms of resilience on PLEs remain elusive. Our finding of a stronger protective effect in affected *vs* non-affected subjects suggests that resilience could be a personal resource particularly important following a natural disaster. It could be carefully speculated that, if on the one hand, resilience is particularly important in long-term protection from natural disasters, other factors could play a protective role in persons not involved in traumatic experiences.

In our results, the resilience factor showing the strongest protective effect was "perception of self", a factor concerning the confidence in one's own abilities, self-confidence, self-efficacy, positive outlook. This is coherent with evidence low self-esteem mediating the effects of childhood adversities on PLEs (5). It is noteworthy that this factor in particular show very different OR between affected and non-affected subjects.

Further studies are needed to explore the pathways through different resilience factors.

Limitations

The present study has several limitations. Firstly, it has a cross-sectional design, hence reports on earthquake impact, especially on psychological suffering, may have been affected by recall bias. However, more objective measures such as material damages should be less sensitive to recall bias. Secondly, a considerable number of people had left the city of L'Aquila, possibly due to long-lasting psychological problems associated with constant re-exposure to traumatic reminders of the earthquake during the last 10 years (39) [based on the authors' personal experience. See also (40)]. This could have introduced a selection bias with the underrepresentation of heavily traumatized subjects. Thirdly, our study was based on voluntary on-line recruitment, that could have introduced a self-selection bias. Finally, our study lacks a measure of post-traumatic symptoms that could have provided further in-depth analysis of the relations between this particular traumatic event and PLEs.

The major limitation of this study is that it lacks a baseline assessment of resilience prior to the earthquake, or any comparable measure of resilience in the general population or in another comparable convenience sample. Moreover, severity of psychological sufferings was not measured using a standardized psychometric instrument.

CONCLUSIONS

This is the first study reporting the very-long term impact of a natural disaster in PLEs in a university student sample of young

adults. No direct effect of the earthquake on PLEs was detected after 10 years after disaster. Resilience could have played a key role in normalizing the psychopathological effect of such a traumatic experience. Further studies are required in order to better characterize individual and contextual determinants of resilience in the face of a traumatic event. Moreover, the evidence of a lack of long-term effect of a natural disaster on PLEs needs to be replicated in different populations.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the internal review board at University of L'Aquila. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, RR, AC, PS, FP, and AR. Methodology: R.R and AC. Software: RR and AC. Formal analysis: RR. Data curation: AC and RR. Writing—original draft preparation: RR. Writing—review and editing: RR, DT, AR, PS, EG, VS, FP and GL.

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Effects Of Early Trauma and Recent Stressors on Depression, Anxiety, and Anger

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Background: Early life traumatic events and recent stressful events are known to have especially strong effects on emotional wellbeing. However, little is known about the interaction of early and recent stressors on emotions. We aimed to examine the interactive effects of early trauma and recent stressors on depression, anxiety, and anger.

Methods: One hundred and seventy adults were recruited and asked to complete the Center for Epidemiological Studies Depression Scale (CES-D), the state anxiety subscale of the State–Trait Anxiety Inventory (STAI-S), and the state anger subscale of the State–Trait Anger Expression Inventory (STAXI-S). Early traumas and recent stressors were assessed during face-to-face interviews. Multiple regression analysis was performed to test whether early trauma, recent stressors, and the interaction of the two would predict CES-D, STAI-S, and STAXI-S scores.

Results: In the multiple regression models, STAI-S scores were predicted only by recent stressors ($R^2 = 0.063$, $p = 0.001$). In contrast, CES-D and STAXI-S scores were predicted only by the synergistic interaction of early trauma with recent stressors ($R^2 = 0.075$, $p < 0.001$; $R^2 = 0.039$, $p = 0.01$, respectively).

Conclusions: A synergistic interaction effect between early trauma and recent stressful events on current depression and anger was observed, indicating that the combined effects of early trauma and recent stressors are stronger than their individual effects. In contrast, anxiety was affected mainly by recent stressors. Our findings suggest that the form that emotional disturbance takes can vary depending on the timing of stressors.

Keywords: depression, anxiety, anger, trauma, stress

INTRODUCTION

Stressful life events can contribute to various emotional disturbances such as depression, anxiety, and anger (1–4). Stressful life events seem to affect emotion *via* various mechanisms, including variations in neurological development, epigenetic modifications, neuroendocrine modulation, or changes in brain circuits (5–12). Recent stressful life events have been suggested to stimulate conditions for subsequent depression, anxiety, or anger (1, 13–17). In addition, early traumatic events are known to have strong, long-term effects on emotional well-being (18, 19), being associated depression, anxiety (20–22), and anger (23, 24). A previous study reported that childhood adversity leads to higher levels of anger and aggression (23). Childhood adversity and anger have also been reported to be associated with neurobiological changes, such as altered activity in the amygdala and dorsolateral prefrontal cortex (24). Recent stressors can also provoke anger (4, 25). Anger is an important issue when studying the emotional effects of trauma or stress, and should be assessed separately from anxiety and depression. The effects of childhood traumatic events on emotional disturbances may continue into adulthood (26).

As stressful events have cumulative effects (27–30), the long-term effect of early trauma and the short-term effects of recent stressors may simply be additive. However, it may also be that the early trauma and recent stressors have synergistic effects on emotional responses such as depression, anxiety, and anger. Given that the neurobiological mechanism by which early life trauma affects subsequent emotion may be different from that for recent stressful life events, these two different mechanisms may have synergistic or interacting effects on the development of emotional disturbances (12).

Also from a psychological viewpoint, children with early adversity exhibit more severe emotional disturbances when they experience subsequent stressful events. Individuals who have experienced trauma during childhood may show emotional dysregulation (31). Emotional regulation plays an important role in coping with stress. Dysfunctional emotion regulation strategies, such as high expressive suppression, are associated with emotional difficulties (32). Childhood traumatic experience can be a risk factor for negative emotions through the mechanism of emotional dysregulation. Individuals with early traumatic experiences may be more likely to exhibit emotional disturbances during subsequent stressful situations (33–36). In other words, childhood traumatic experience can exacerbate the emotional disturbances caused by subsequent stressful life events (37, 38).

Several studies have investigated both early trauma and recent stressors in a single study. However, only few have explored the interactive effects of early trauma and recent stressors on depression, and those produced controversial results. One study reported the interactive effects of childhood adversity and recent life stressors on suicidal behavior among Chinese college students (39). Others reported that young Americans (37) and psychiatric outpatients in Germany (38) who reported childhood adversity became more depressed after experiencing recent stressors. However, another study found no effect of the interaction between early and recent stressors on depression in older people (26). These discrepancies may be due to differences in sample characteristics, such as age or psychiatric illness. Furthermore, no studies have investigated such interactive effects on anxiety or anger.

In the current study, we aimed to explore the effects of early trauma, recent stressors, and their interaction on depression, anxiety, and anger in a community sample covering a broad range. We hypothesized that the interaction between early trauma and recent stressors would exert a synergistic effect on subsequent depression, anxiety, and anger. In other words, early trauma is posited to exacerbate the effects of recent stressors, thus promoting emotional disturbances, while recent stressors should in turn exacerbate the effects of early trauma.

METHODS

Subjects

Community-dwelling adults (≥19 years of age) were recruited in the Incheon area, which is the third largest metropolitan area in South Korea. Participants were recruited through posters and brochures placed in hospitals, apartment buildings, churches, and public health centers. All participants were asked to self-report their levels of depression, anxiety, and anger.

A total of 170 subjects participated in the study, including 73 men and 97 women. The mean age of subjects was 41.1 ± 8.2 years; there was no significant difference in age between men and women (**Table 1**).

The study protocol was approved by the institutional review board of Gachon University of Medicine and Science. All subjects provided written informed consent.

Assessment of Early Trauma and Recent Stressors

Information on early trauma was collected through face-to-face interviews using the Early Life Stress Questionnaire (ELSQ). ELSQ is a questionnaire based on the Child Abuse and Trauma Scale (40). With ELSQ, responders are asked to indicate whether they experienced any of 19 negative events, such as physical and sexual abuse and neglect, in early life (41).

Information regarding recent negative stressors was also obtained through face-to-face interviews. During the interview, subjects were asked whether any of the items extracted from the Life Experience Survey (LES) described their own experience. The questions asked about (1) bereavement involving family or close friends; (2) serious illness in oneself or a family member; (3) serious economic crisis; (4) unwanted retirement or being fired; (5) severe conflicts with family, friends, relatives, or colleagues; and (6) divorce or unwanted end of a relationship (42, 43). To minimize the possibility of recall bias, participants were asked to report only experiences that had happened during the 6 months prior to their participation in the study.

All subjects were divided into four groups based on the presence of early trauma and/or recent stressors: those with both early trauma and recent stressors (ET-RS); those with early trauma but no recent stressors (ET-NRS); those with recent

TABLE 1 | Comparison of depression, anxiety, and anger Between subjects with and without early trauma or recent stressors.

	ET-RS (*n* = 16) Mean ± S.D., *n* (%)	ET-NRS (*n* = 49) Mean ± S.D., *n* (%)	NET-RS (*n* = 24) Mean ± S.D., *n* (%)	NET-NRS (*n* = 81) Mean ± S.D., *n* (%)	Total (*n* = 170) Mean ± S.D., *n* (%)	Post hoc
Demographic variables						
Age (year)	41.9 ± 8.1	39.6 ± 7.0	41.8 ± 6.1	41.6 ± 9.4	41.1 ± 8.2	–
Gender (male)	5 (31.3%)	26 (53.1%)	9 (37.5%)	33 (40.7%)	73 (42.9%)	–
Depression						
CES-D score*	19.4 ± 12.8	11.7 ± 8.2	12.1 ± 10.3	10.1 ± 8.0	11.7 ± 9.2	ET-RS > ET-NRS, NET-NRS
Anxiety						
STAI-S score*	53.0 ± 7.6	48.7 ± 6.5	51.6 ± 8.1	46.9 ± 7.8	48.7 ± 7.7	ET-RS, NET-RS > NET-NRS
Anger						
STAXI-S score	14.8 ± 6.0	13.3 ± 4.6	13.0 ± 5.7	11.9 ± 3.3	12.7 ± 4.4	–

ET-RS, those with both early trauma and recent stressors; ET-NRS, those with early trauma but without recent stressors; NET-RS, those with recent stressors but without early trauma; NET-NRS, those with neither early trauma nor recent stressors; CES-D, Center for Epidemiological Studies-Depression Scale; STAI-S, state anxiety subscale of the Korean version of the State–Trait Anxiety Inventory; STAXI-S, state anger subscale of the Korean version of the State–Trait Anger Expression Inventory.
**p < 0.05 on the Kruskal–Wallis test.*

stressors but no early trauma (NET-RS); and those with neither early trauma nor recent stressors (NET-NRS). Subjects were also divided into two groups according to the presence/absence of early trauma and the presence/absence of recent stressors, independently of whether they had experienced the other form of stressor.

Assessments of Emotional Disturbances

To measure depressive symptoms, the Korean version of the Center for Epidemiological Studies Depression Scale (CES-D) was used. The severity of depression is reflected in CES-D scores, with higher scores indicating more severe depression. The Korean version of the CES-D is well verified. It consists of 20 questions and has an internal reliability coefficient of 0.89. The Korean version of the CES-D tends to produce higher scores than the original version (44, 45).

The Korean version of the State–Trait Anxiety Inventory (STAI) was used to measure current anxiety. A high score indicates high levels of anxiety. STAI is divided into subscales assessing state anxiety (the current anxiety level) and trait anxiety (intrinsic emotional characteristics (46, 47). In this study, the state anxiety subscale (STAI-S) was used to measure the current anxiety level. The scale comprises 20 questions designed to measure state anxiety, and has an internal reliability coefficient of 0.87.

The Korean version of the State–Trait Anger Expression Inventory (STAXI) was used to measure current anger. High scores indicate more severe anger symptoms. As with STAI, STAXI is divided into subscales assessing state and traits (48, 49). We used the state anger subscale (STAXI-S) to measure current anger in this study. This questionnaire consists of 24 questions and has an internal reliability coefficient of 0.89.

Statistical Analysis

Independent t-tests and Pearson's correlations were used to compare continuous variables, and chi-square tests to compare categorical data. Non-parametric statistical tests such as the Kruskal–Wallis test or the Mann–Whitney U-test were used when it was not possible to assume regularity based on the Kolmogorov–Smirnov test. Stepwise multiple regression analysis was performed to test whether the interaction between early trauma on ELSQ (ET) and recent stressors on LES (RS) was a statistically significant predictor of CES-D, STAI-S, and STAXI-S scores. The dependent variables were CES-D, STAI-S, and STAXI-S scores. The independent variables were age, gender, ET, RS, and ET × RS. ET × RS was added as an independent variable to test the interaction of early trauma and recent stressors. The depressed group included subjects with a CES-D score ≥ 16; those with a score of ≤ 15 were classified into the non-depressed group. A regression analysis was performed on the depressed and non-depressed groups. SPSS Statistics ver. 25 was used for statistical analysis.

RESULTS

Characteristics of the Study Subjects

In total, 170 subjects participated in the current study. Among them, 73 (42.9%) were men. There were no statistically significant sex differences in CES-D, STAI-S, or STAXI-S scores. The mean age of subjects was 41.1 ± 8.2 years. Age was not significantly correlated with CES-D, STAI-S, or STAXI-S scores (**Table 1**). There was no significant difference in age or sex between those with and without early trauma or between those with and without recent stressors. There was no significant association between the presence of early trauma and the occurrence of recent stressors.

Sixty-five (38.2%) subjects reported early traumatic experiences, and 40 (23.5%) reported recent stressful life events. Sixteen subjects (9.4%) were included in the ET-RS group, 49 (28.8%) in the ET-NRS group, 24 (14.1%) in the NET-RS group, and 81 subjects (47.6%) were included in the NET-NRS group (**Table 1**).

For all subjects, the mean (± SD) CES-D score was 11.7 ± 9.2, and the mean STAI-S and STAXI-S scores were 48.7 ± 7.7 and 12.7 ± 4.4, respectively (**Table 1**). Fifty-two subjects with a score ≥ 16 on the CES-D were assigned to the depressed group. CES-D was significantly correlated with both STAI-S ($r = 0.658$, $p < 0.001$) and STAXI-S ($r = 0.564$, $p < 0.001$) scores. The STAI-S and STAXI-S scores were also significantly correlated ($r = 0.482$, $p < 0.001$).

Effects of Early Trauma and Recent Stressors on Depression

The mean CES-D score of those who had experienced early trauma was significantly higher than that of subjects who had not (U = 2759.500, p = 0.036). Similarly, those who had experienced recent stressors had higher mean CES-D scores than those who had not (U = 2020.000, p = 0.033). The mean CES-D scores for the four groups were as follows: ET-RS, 19.4 ± 12.8; ET-NRS, 11.7 ± 8.2; NET-RS, 12.1 ± 10.3; NET-NRS, 10.1 ± 8.0 (**Table 1**). The difference among the groups was significant (H = 9.995, p = 0.019). Post hoc tests showed that the mean CES-D score of the ET-RS group was significantly higher than that of the ET-NRS (U = 245.500, p = 0.026) and NET-NRS groups (U = 332.500, p = 0.002) (**Figure 1A**). In the multiple regression models, the CES-D score was predicted by the interaction of early trauma and recent stressors (R^2 = 0.075, p < 0.001), but not by early trauma or recent stressors alone (**Table 2**). Similar results were found in the regression model after logarithmic transformation of CES-D.

Effects of Early Trauma and Recent Stressors on Anxiety

Participants who had experienced recent stressors had higher average STAI-S scores than those who had not (t = 3.374, p = 0.001). Early trauma, however, had no significant effect on anxiety. The mean STAI-S scores in the four groups were as follows: ET-RS, 53.0 ± 7.6; ET-NRS, 48.7 ± 6.5; NET-RS, 51.6 ± 8.1; and NET-NRS, 46.9 ± 7.8 (**Table 1**). The difference among the groups was significant (H = 12.279, p = 0.006). Post hoc tests showed that the mean STAI-S scores of the ET-RS (U = 358.500, p = 0.005) and NET-RS groups (U = 647.500, p = 0.013) were significantly higher than that of the NET-NRS group (**Figure 1B**). In the multiple regression model, the only significant predictor of STAI-S scores was recent stressors (R^2 = 0.063, p; = 0.001) (**Table 2**). This result did not change with logarithmic transformation of STAI-S scores.

Effects of Early Trauma and Recent Stressors on Anger

Participants who had experienced early trauma had higher STAXI-S scores than those who had not (U = 2826.000, p = 0.048). However, recent stressors showed no significant effect on anger. The mean STAXI-S scores in the four groups were as follows: ET-RS, 14.8 ± 6.0; ET-NRS, 13.3 ± 4.6; NET-RS, 13.0 ± 5.7; and NET-NRS, 11.9 ± 3.3 (**Table 1**). Overall, the groups did not differ significantly (**Figure 1C**), but a direct comparison of the ET-RS and NET-NRS groups revealed a significant difference (U = 440.000, p = 0.033). No other group differences were found. STAXI-S scores were predicted by the interaction of early trauma with recent stressors (R^2 = 0.039, p = *0.010)*, but not by early trauma or recent stressors alone (**Table 2**). After logarithmic transformation of STAXI-S scores, similar results were found in the regression model.

Predictors of Questionnaire Scores According to Depression Status

The CES-D scores of the depressed group were predicted by the interaction between early trauma and recent stressors (R^2 = 0.096, p = *0.025*), but not by early trauma or recent stressors alone. No variables significantly predicted the STAI-S or STAXI-S scores in the depressed group. In contrast, the STAI-S scores of the non-depressed group were significantly predicted by recent stressors (R^2 = 0.065, p = *0.005*). No other variables significantly predicted the CES-D or STAXI-S score in the non-depressed group.

DISCUSSION

The current study investigated the effect of early trauma, recent stressors, and their interaction on depression, anxiety, and anger in a community sample representing a broad age range. The results varied with the type of emotional disturbance examined.

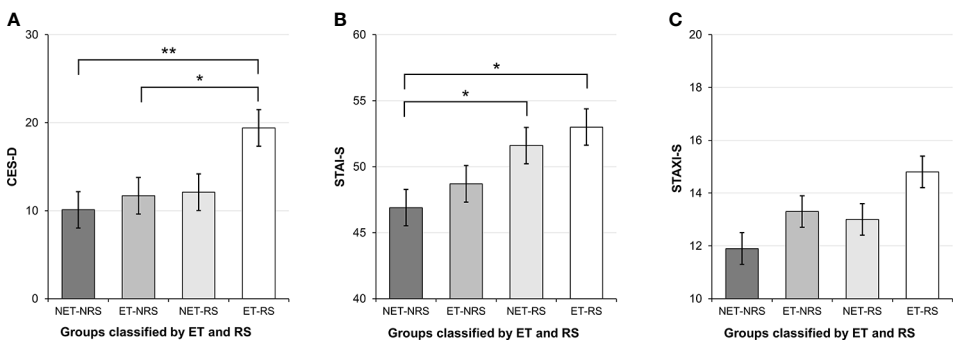

FIGURE 1 | Depression, anxiety, and anger among subjects with or without early trauma and/or recent stressors. ET, presence of early trauma on the Early Life Stress Questionnaire; RS, presence of recent stressors on the Life Experience Survey; ET-RS, those with both early trauma and recent stressors; ET-NRS, those with early trauma but without recent stressors; NET-RS, those with recent stressors but without early trauma; NET-NRS, those with neither early trauma nor recent stressors; CES-D, Center for Epidemiological Studies-Depression Scale; STAI-S, state anxiety subscale of Korean version of State–Trait Anxiety Inventory; STAXI-S, The state anger subscale of the Korean version of the State–Trait Anger Expression Inventory. *p < 0.05, **p < 0.005. **(A)** Depression classified according to ET and RS. **(B)** Anxiety classified according to ET and RS. **(C)** Anger classified according to ET and RS.

TABLE 2 | Effects of early trauma, recent stressors, and the early trauma–recent stressors interaction on depression, anxiety, and anger.

	R^2	Age	Gender	ET	RS	ET x RS
CES-D score	0.075	–	–	–	–	β = 2.881***
STAI-S score	0.063	–	–	–	β = 4.560**	–
STAXI-S score	0.039	–	–	–	–	β = 0.994*

ET, presence of early trauma on the Early Life Stress Questionnaire; RS, presence of recent stressors on the Life Experience Survey; CES-D, Center for Epidemiological Studies-Depression Scale; STAI-S, state anxiety subscale of the Korean version of the State–Trait Anxiety Inventory; STAXI-S. state anger subscale of the Korean version of the State–Trait Anger Expression Inventory.
**p < 0.05, **p < 0.005, ***p < 0.001.*

Depression and anger were mainly predicted by the interaction of early trauma and recent stressors, supporting our *a priori* hypothesis. However, contrary to our hypothesis, anxiety was predicted only by recent stressors and not by the early trauma–recent stressor interaction.

As expected, in the current study, both early trauma and recent stressors were associated with greater depression. When subjects were divided into four groups based on the presence or absence of early trauma and recent stressors, those who reported both early trauma and recent stressors were more depressed than those who had experienced only early trauma. Furthermore, depressive symptoms were predicted only by the interaction between early trauma and later stressors. The current findings suggest that depressive mood may be affected by synergistic effects of past childhood trauma and a current stressful environment.

Our finding corresponds to the stress sensitization model of depression, which proposes that the first depressive episode makes the individual more prone to subsequent depressive episodes following stressors (50, 51). Recently, stress itself has been suggested to produce sensitization for depression. According to this sensitization model, people who experienced early trauma are more easily depressed when they experience later stressors (37). Those without early trauma can fend off depression even under currently stressful conditions, and those with early trauma experiences can avoid depression if they are not currently experiencing stress.

The current findings correspond to those of previous studies reporting synergistic effects of early trauma and later stressors on the development of depression in young populations (37, 38). However, one study reported that childhood adversity did not modify the effect of recent events on depression of people 55–85 years of age (26). These discrepancies in findings may be due to differences between populations. The effect of early traumatic events may diminish as people get older, due to the longer time since the event rather than to age itself. Post-traumatic stress disorder (PTSD) symptoms after trauma tend to decrease with time, although there are some exceptions to this. Psychiatric symptoms caused by trauma decrease over time in veterans (52), young adults (53), and children (54). In addition, memories of a trauma tend to be vary depending on when they are evaluated (55, 56); thus, it appears that traumatic memories can change significantly over time. As the mean age of participants in our study was 41 years, our results suggest that the interactive effects of early trauma and current stress on depression might persist through middle age.

In the current study, as expected, anxiety was affected by recent stressors; however, it was not affected by early trauma (14, 16). The absence of a relationship between early trauma and current anxiety was contrary to previous findings showing that childhood adversity is linked to anxiety in adults (20, 57, 58). This discrepancy may reflect differences among studies in the severity of childhood trauma. Most previous studies focused on more serious trauma, such as physical or sexual abuse, whereas ours included any childhood adversity reported on the ELSQ. In addition, compared to depression or anger, anxiety may be highly affected by the present situation. Moreover, adulthood anxiety in victims of early trauma has been reported to vary depending on the person's resilience (59–61). Those with low resilience become sensitized to emotional difficulties by childhood adversity, whereas others may even achieve posttraumatic growth after similar experiences (62, 63).

Anger was predicted only by the interaction between early trauma and recent stressors. Anger, like depression, is likely to be provoked when people who experienced childhood trauma encounter subsequent negative life events. Experiences of childhood trauma might result in a character structure that makes it easier to feel angry in stressful situations (24).

Although statistical insignificance necessarily means no real effects, some of the results in this study lost significance when the participants were divided into the depressed and non-depressed groups. The synergistic effects of early trauma and recent stressors on depression were found only in the depressed group. In contrast, the effects of recent stressors on anxiety were more prominent in the non-depressed group. These findings suggest that the interaction effect between early trauma and recent stressors on depression may be stronger in depressed than non-depressed groups. Non-depressed people may respond to current stress with anxiety, regardless of past childhood traumatic experience.

Usually, the CES-D is used for psychopathological evaluation of symptoms of depressive disorder while the STAI-S and STAXI-S are concerned with emotional problems. Our results may be related to the different dimensions measured by the questionnaires. The psychopathological problems measured by the CES-D may be more affected by the synergistic interaction between early trauma and recent stressors, while the emotional responses measured by the STAI-S are more related to current stressful events. However, we found that the STAXI-S scores were also associated with the synergistic interaction between early trauma and recent stressors, similar to the CES-D which is psychopathological evaluation. These complex results may be due to the infeasibility of distinguishing between psychopathological and emotional aspects in many situations. Severe anxiety or anger may be not only problematic but also pathological by themselves.

Previous studies have shown the effects of the interaction between early trauma and recent stressors on depression or suicidality in younger groups (37–39). To the best of our knowledge, the current study is the first to explore the

interaction effect between early trauma and recent stressors on negative emotions such as anxiety or anger in a community sample with a wide age range.

The current study found that the effects of early and recent stressors and their interaction varied with the type of emotional disturbance considered. This finding may have some clinical implications. When individuals with early trauma encounter new stressful events, special clinical attention should be paid to the development or aggravation of depression or anger. For the management of anxiety, focusing on and coping with current stressful events rather than early experiences would be more helpful.

This study has several limitations. First, the number of subjects, especially of individuals who experienced recent stressors, was small. Thus, the impact of recent stressors may have been underestimated. Besides, convenience sampling was used to recruit the subjects. Thus, the generalizability of the result may be limited. Second, given that the information about early and recent stressors was obtained only by self-report, the data may be subject to recall bias or selective reporting and attempts to hide shameful or painful memories. Third, PTSD disease group was not analyzed separately. However, there were no subjects who reported diagnosis of PTSD at the time of the investigation. Besides, traumatic experiences do not always lead to PTSD (64). Especially, the ELSQ covers mild as well as severe traumatic experiences. The possibility of the recall bias of the early childhood experience would also be considered. Fourth, as this study was cross sectional, it could not show causal relationships or the mechanism underlying stressor interactions and their effects on emotions. Fifth, because stressful events were measured only in terms of their presence or absence, differences among individuals in the nature and severity of those experiences could not be considered. A future cohort study examining the detailed nature of such events in a large population may be needed to confirm the interaction effects of early and recent stressors on emotions.

In conclusion, our results showed a synergistic interaction between early trauma and recent stressors on current depression and anger. Anxiety, however, was affected mainly by recent stressors in the present study. Clinicians should be aware that clients' emotional difficulties may depend on when they experienced traumatic or stressful experiences.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by institutional review board of Gachon University of Medicine and Science. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: SK, S-JC. Data curation: SK, S-JC, YL, JL, BS. Formal analysis: SJ, BS. Funding acquisition: SK. Investigation: SK, BS. Methodology: SK, S-JC, YL, JL, BS. Project administration: SK. Resources: SK, S-JC, YL. Supervision: SK. Software: YL, BS. Validation: SJ, JL. Visualization: BS. Writing—original draft: BS. Writing—review and editing: SJ, SK.

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Neonatal Tactile Stimulation Alters Behaviors in Heterozygous Serotonin Transporter Male Rats: Role of the Amygdala

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The serotonin transporter (SERT) gene, especially the short allele of the human serotonin transporter linked polymorphic region (5-HTTLPR), has been associated with the development of stress-related neuropsychiatric disorders. In line, exposure to early life stress in SERT knockout animals contributes to anxiety- and depression-like behavior. However, there is a lack of investigation of how early-life exposure to beneficial stimuli, such as tactile stimulation (TS), affects later life behavior in these animals. In this study, we investigated the effect of TS on social, anxiety, and anhedonic behavior in heterozygous SERT knockouts rats and wild-type controls and its impact on gene expression in the basolateral amygdala. Heterozygous SERT$^{+/-}$ rats were submitted to TS during postnatal days 8–14, for 10 min per day. In adulthood, rats were assessed for social and affective behavior. Besides, brain-derived neurotrophic factor (Bdnf) gene expression and its isoforms, components of glutamatergic and GABAergic systems as well as glucocorticoid-responsive genes were measured in the basolateral amygdala. We found that exposure to neonatal TS improved social and affective behavior in SERT$^{+/-}$ animals compared to naïve SERT$^{+/-}$ animals and was normalized to the level of naïve SERT$^{+/+}$ animals. At the molecular level, we observed that TS *per se* affected Bdnf, the glucocorticoid-responsive genes Nr4a1, Gadd45β, the co-chaperone Fkbp5 as well as glutamatergic and GABAergic gene expression markers including the enzyme Gad67, the vesicular GABA transporter, and the vesicular glutamate transporter genes. Our results suggest that exposure of SERT$^{+/-}$ rats to neonatal TS can normalize their phenotype in adulthood and that TS *per se* alters the expression of plasticity and stress-related genes in the basolateral amygdala. These findings demonstrate the potential effect of a supportive stimulus in SERT rodents, which are more susceptible to develop psychiatric disorders.

Keywords: neonatal period, tactile stimulation, anxiety, Bdnf, serotonin transporter knockout, amygdala

INTRODUCTION

Vulnerability to psychiatric disorders is thought to be caused by complex interactions between genes and the environment particularly when the interactions take place early in life (Caspi et al., 2010). The serotonin transporter linked polymorphic region (5-HTTLPR) serves as a model for gene-environment interactions, with the short (s) 5-HTTLPR allele playing an important role in the sensitivity to the environment (Homberg and Lesch, 2011; Homberg et al., 2016). In rodents, these behavioral conditions can be evaluated in serotonin transporter (SERT) knockout rats (Homberg et al., 2007). Heterozygous SERT knockout animals ($SERT^{+/-}$) are generally suggested to be most comparable to the human short 5-HTTLPR allele from a gene-dose dependent point of view. Although some studies could not confirm an interaction effect of SERT genotype and early life adversities (see review: Houwing et al., 2017), other studies have shown a significant influence of the $SERT^{+/-}$ genotype on behaviors putatively related to psychiatric disorders (Olivier et al., 2008; Bartolomucci et al., 2010; van der Doelen et al., 2013; Houwing et al., 2019).

SERT knockout animals present enhanced anxiety- and depression-like symptoms (Homberg et al., 2008; Schipper et al., 2015, 2019; Verheij et al., 2018) and most studies examined the increased sensitivity to negative environmental stimuli in SERT knockout rodents. However, a few studies demonstrated that these animals are also very sensitive to positive environmental stimuli such as psychostimulants, conditioned reward, co-housing with a female, and environmental enrichment (Homberg and Lesch, 2011; Nonkes et al., 2012; Kastner et al., 2015; Homberg et al., 2016; Rogers et al., 2017). This is well in line with the differential susceptibility theory from the field of developmental psychology, which postulates that "plastic" individuals, due to (5-HTTLPR s/s) genotype, show increased sensitivity to environmental stimuli, both adverse and supportive ones (Belsky et al., 2009; van Ijzendoorn et al., 2012).

Early life is a critical phase for central nervous system development, during which plasticity levels are high and the brain is very sensitive to environmental influences. Thus far, no studies have addressed the effect of an early life supportive environment on later life behavior in $SERT^{+/-}$ rodents. Neonatal handling is an environmental treatment used to study behavioral mechanisms and neurobiological alterations in rodents (Denenberg, 1964). The handling consists of separating the pups from the mothers for a short period and performing some intervention, such as tactile stimulation (TS; Daskalakis et al., 2009). Neonatal TS is a procedure applied during developmental periods mimicking nonspecific maternal stimulation such as licking and grooming of pups. It has emerged as an efficient tool to improve the behavior by altering brain organization and enhancing hippocampus neurogenesis (Guerrero et al., 2016) and neuroplasticity (Richards et al., 2012). TS decreases anxiety-like behaviors (Río-Alamos et al., 2015), and prevents the negative effects of stress (Boufleur et al., 2013) and the development of depressive-like behaviors (Freitas et al., 2015). These findings raise the possibility that TS has the potential to modify the anxiety- and depression-related phenotypes of $SERT^{+/-}$ animals.

The TS mechanism in the brain is still unclear, but evidence has suggested that TS affects the hypothalamic-pituitary-adrenal (HPA) axis and brain neurotrophic factors such as brain-derived neurotrophic factor (Bdnf; Antoniazzi et al., 2017; Roversi et al., 2019). Further, the GABA and glutamate systems are likely targets. The HPA-axis mediates stress responses through glucocorticoids release from the adrenal cortex. The programming of the HPA-axis is influenced by stress, leading to glucocorticoid receptor (Nr3c1) dysregulation and changes in the expression of glucocorticoid-inducible genes, including the co-chaperone FK506-binding protein 51 (Fkbp5) and the transcription factor Nr4a1 (Kember et al., 2012; van der Doelen et al., 2014). Indeed, the expression of Fkbp5 was found to be altered in peripheral blood cells of patients suffering from psychiatric disorders following early life adversities (Klengel et al., 2013). Furthermore, altered stress-related behavior in adulthood has been associated with changes in Nr4a1 gene expression in the hippocampus of mice (Kember et al., 2012). Also, the growth arrest and DNA-damage-inducible beta (Gadd45β), a glucocorticoid-responsive gene responsible for actively demethylating gene promoter regions, was found to be increased in the hippocampus of rats treated with the multitarget antidepressant vortioxetine and exposed to acute stress (Brivio et al., 2019). Finally, negative experiences in early life seem to affect the levels of Gadd45β, yet also overexpression of this gene has been observed in the amygdala of psychiatric patients (Gavin et al., 2012; Blaze and Roth, 2013). Thus, whether Gadd45β is also responsive to positive stimuli in early life remains to be determined.

Bdnf is a molecule that promotes the development and survival of neurons and is present in high amounts in the basolateral amygdala. Changes in Bdnf levels in this area are associated with stress-dependent learning and important behavioral changes related to fear and depression (Williams et al., 2006; Schulte-Herbruggen et al., 2006). While TS increased Bdnf hippocampus levels and improved memory and anxiety behaviors in normal and depressive-like animals (Antoniazzi et al., 2017; Roversi et al., 2019), transgenic overexpression of Bdnf in the amygdala facilitated the development of anxiety-related behaviors (Govindarajan et al., 2006), thus showing the importance of the modulatory effect of Bdnf in the brain. Neonatal handling also affects the GABAergic system, as demonstrated by increased GABA interneuron density in the lateral amygdala (Giachino et al., 2007). Moreover, there is an important link between the GABAergic and glutamatergic systems in animal models of depression and different stress-related psychiatric disorders (Garcia-Garcia et al., 2009; Luscher et al., 2011), such as depression, which is characterized by an excitation-inhibition imbalance (Sanacora et al., 2004). Furthermore, expression levels of Gad67, the enzyme that converts glutamate in GABA, are decreased in psychiatric disorders (Fatemi et al., 2005). Conversely, positive stimuli like environmental enrichment that can buffer the negative effects of stress also alter GABAergic signaling in the amygdala (Sampedro-Piquero et al., 2016). Finally, there is evidence

that Bdnf affects the excitation-inhibition balance, providing a putative pathway through which positive environmental stimuli may ameliorate stress-induced excitation-inhibition imbalances (Oh et al., 2016).

In this study we sought out to determine the effect of a supportive environment, that is TS, during the postnatal day (PND) 8–14. This period of life was chosen based on a previous study of Antoniazzi et al. (2017), in which the most beneficial effects of TS have been observed during this period. Furthermore, in rats, brain development paces extremely fast during the first weeks of life. Neurogenesis is completed on PND 15 (Rice and Barone, 2000; Babikian et al., 2010), the astrocytes undergo to a rapid period of maturation, with a peak on PND 11–16 (Catalani et al., 2002), and the critical period of synaptogenesis peaks during week 2 after birth (Semple et al., 2013). As readouts we focused on social behavior, anhedonia, and anxiety in SERT$^{+/-}$ and wild-type control rats in adulthood. Additionally, to understand the underlying mechanisms we assessed mRNA expression levels of Bdnf, glucocorticoid (Nr3c1) and mineralocorticoid (Nr3c2) receptors, and glucocorticoid-responsive genes in the basolateral amygdala. We also focused on components of the GABAergic and glutamatergic systems, by analyzing Gad67, vesicular GABA transporter (Vgat), parvalbumin, and vesicular glutamate transporter (Vglut) gene expression.

MATERIALS AND METHODS

Animal and Procedures

Eight wild-type and eight SERT$^{+/-}$ (Slc6a41Hubr) pregnant rats were used. They were derived by crossing heterozygous breeding animals. Dams were checked daily for pups' delivery, and the day of birth was set as postnatal day (PND) 0. On PND8–14, male pups from each litter were assigned to one of the two experimental groups: neonatal TS or not (no TS, naïve), and the pups were marked with a non-toxic colored marker for identification purposes. At PND21, pups were weaned, and ears were punched for identification and genotyping (Homberg et al., 2007). The animals were housed in two animals per cage, in standard polypropylene cages with saw-dust bedding and water and food *ad libitum*, in a temperature (21 ± 1°C) and humidity-controlled room (45%–60% relative humidity), with a 12:12 h light/dark cycle (lights on at 7:00 AM). The experimental procedures were approved by the Committee for Animal Experiments of the Radboud University Nijmegen, The Netherlands, and all efforts were made to minimize animal suffering and to reduce the number of animals used. Only male SERT$^{+/-}$ rats were used in this study. At PND 60, the males from naïve and TS were subdivided between treatment and genotype [wild-type (SERT$^{+/+}$) or heterozygous (SERT$^{+/-}$)] groups, resulting in the following groups: naïve SERT$^{+/+}$ (n = 9); naïve SERT$^{+/-}$ (n = 7); TS SERT$^{+/+}$ (n = 9); TS SERT$^{+/-}$ (n = 9; **Figure 1A**). All tests were performed in the dark phase.

Neonatal Tactile Stimulation

Neonatal TS was applied from PND 8 to PND 14, between 10 AM and 2 PM. Pups were removed from the nest, gently held by the experimenter, and stroked with the index finger on the dorsal surface, in the rostral-caudal direction for 10 min, once a day. At the end of the TS, pups were returned to their litters. The naïve group (no TS) remained in their nest without any touch by human hands (Freitas et al., 2015; Antoniazzi et al., 2017).

Behavioral Procedures

Social Interaction Test

The social interaction test protocol is based on social interest and interaction with an unfamiliar animal. The arenas consisted of a black floor and transparent walls (45 cm × 50 cm). Before the test, animals were put individually in the chamber for a 1-h habituation session and immediately after habituation, two rats from different cages with the same genotype and manipulation were put together in the arena and the behavior was video recorded for 15 min. The recorded behavior was measured as social contact (time animals spent in body-contact, sniffing, grooming), social interest (time animal was following or approaching), social undergoing (passive behavior: when the rat's partner was mounting, sniffing, pinning, attacking the rat), and non-social behavior (time animal was solitary). One observer blind to the test subjects' genotype and manipulation, manually scored video recordings by using Boris v.7. Both animals were equally observed. By using a reliability analysis feature in Boris (Behavioral Observation Research Interactive Software), the percentages of agreement between two observers were calculated and resulted in 78% of agreement (data not shown).

Elevated Plus-Maze

This test is based on the innate fear rodents have for open and elevated spaces and was performed as described by de Jong et al. (2006). The apparatus consisted of a plus-shaped platform elevated 50 cm from the floor. Two opposite arms (50 cm × 10 cm) were enclosed by 40 cm high walls whereas the other two arms had no walls. The four arms had at their intersection a central platform, which gave access to any of the four arms. At the beginning of each test, the rat was placed on the central platform facing an open arm. The movements and position of the animals were recorded and processed afterward using EthoVision XT (Noldus Information Technology, The Netherlands). Entries were counted when all four paws were placed in one of the arms. Data were expressed as the mean percentage of the time spent on open arms [(time on open arms/300 s) × 100%], the mean of the entries number into open arms [(entries on open arms/total entries) × 100%] and the time spent on closed arms (s). The mean of the time spent (s) on and number of entries to open arms were used as the standard anxiety indices. Locomotor activity was expressed as the total distance moved (cm) by the animal in the entire maze.

Sucrose Consumption

Anhedonia is typically measured using the sucrose consumption test in which the animals have in their homecage a free choice between a bottle with water and a bottle with a sucrose solution. A decrease in sucrose intake and/or preference is considered as a measure of anhedonia (Willner et al., 1987). Animals were housed individually and habituated to the two-bottle paradigm by offering them water in two plastic drinking bottles, one

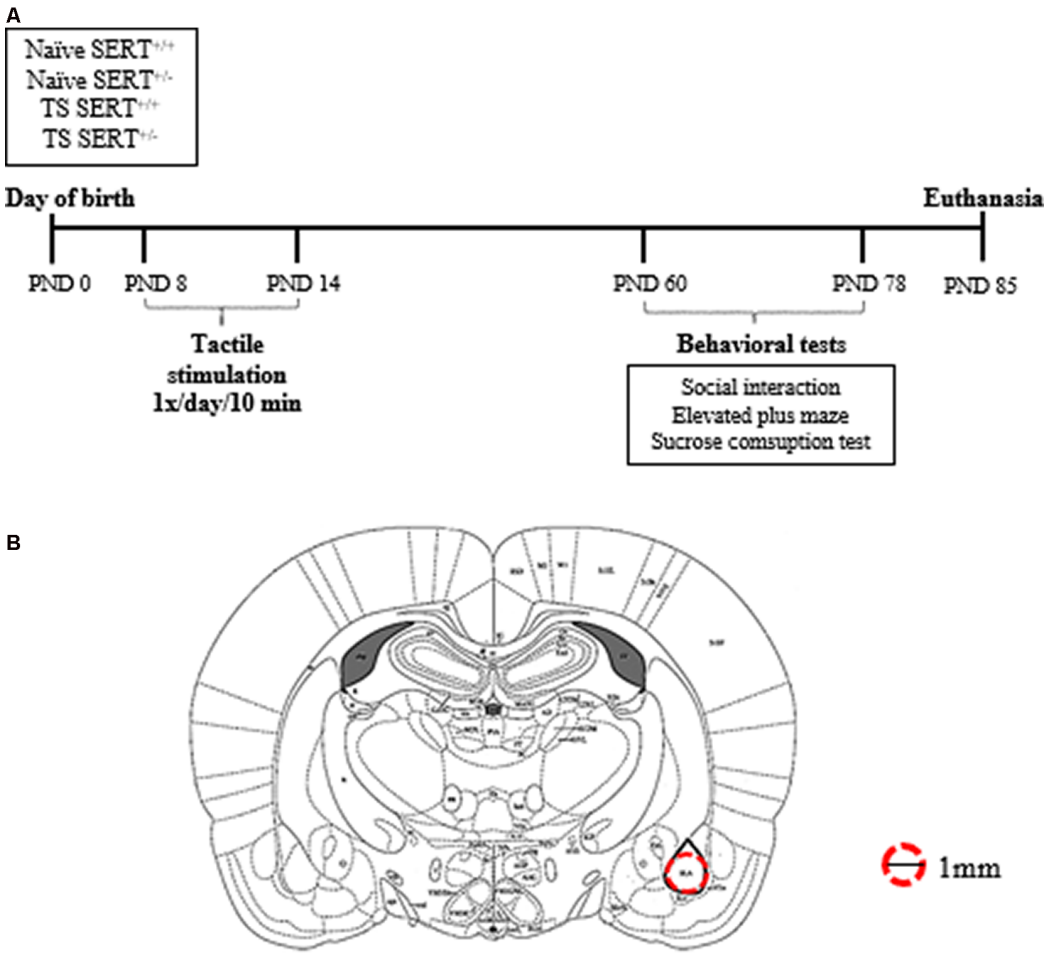

FIGURE 1 | Schematic representation of the experimental paradigm performed in heterozygous serotonin transporter knockout ($SERT^{+/-}$) and wild-type ($SERT^{+/+}$) male rats exposed daily to tactile stimulation (TS) from postnatal day (PND) 8–14 or a control treatment (no TS-naïve; **A**). Diagrams represent the location where basolateral amygdala punches were taken for molecular analyses (adapted from Paxinos and Watson brain Atlas; **B**).

on each side, for a total of 3 days. After the third day of the habituation period, the sucrose test started. Animals were presented with two bottles, one containing water and the other one containing a 3% sucrose solution. Fluid consumption (g) was measured at 2 h, 5 h, and 24 h, and body weight was measured daily (g). Both measures were used to calculate sucrose preference (sucrose intake in ml divided by total intake × 100%) and the intake in grams relative to body weight in Kg (intake in grams divided by body weight in grams/1,000; adapted from Olivier et al., 2008).

Tissue Collection and Preparation

One week after the last day of the sucrose test, the animals were euthanized by decapitation within 10 s. Immediately after the decapitation, the brains were isolated and frozen on dry ice in an aluminum foil and stored in a −80° C. The brains were prepared in 200 μm thick coronal slices in a cryostat (−11°C) to obtain punches of basolateral amygdala bilaterally (Bregma ≈ −2.28: −3.30 mm; Interaural ≈ −6.72: −5.80 mm; anterior-posterior ≈2.8 posterior to bregma; DV ≈6.5 from skull surface) using a 1.00 mm brain puncher (**Figure 1B**). The brain puncher was cleaned with alcohol after each punch. The punches were used for RNA isolation.

RNA Preparation and Gene Expression Analysis by Quantitative Real-Time RT-PCR

Total RNA was isolated from the basolateral amygdala using PureZol RNA isolation reagent (Bio-Rad Laboratories S.r.l.; Segrate, Italy) following the manufacturer's instructions. The RNA concentration was then quantified by spectrophotometric analysis (OD 260/280 1.8 < ratio <2). Afterward, the samples were prepared for real-time polymerase chain reaction (RT-PCR) to measure the mRNA expression of total Bdnf, Bdnf long 3' UTR, Bdnf isoforms IV and VI, Nr3c1, Nr3c2, Nr4a1, Gadd45β, Fkbp5, Gad67, Pvalb, Vgat, Vglut. After RNA isolation, an aliquot of each sample was treated with DNAse to avoid contamination by DNA. The samples were then prepared for the analyses by TaqMan qRT-PCR instrument (CFX384

real-time system, Bio-Rad Laboratories S.r.l.) using the iScript one-step RT-PCR kit for probes (Bio-Rad Laboratories S.r.l.). The primers and probes sequences used were acquired from Eurofins MWG-Operon and Life Technologies and are shown in **Table 1**. The samples (10 ng/ul) were run in a 348-well format in triplicates as multiplexed reactions with the normalizing internal control 36b4. Thermal cycling started with incubation at 50°C for 10 min (RNA retrotranscription), and 95°C for 5 min (TaqMan polymerase activation). After this step, 39 cycles of PCR were performed. Each PCR cycle consisted of heating the samples at 95°C for 10 s to facilitate the melting process and then at 60°C for 30 s for the annealing and extension reactions. A comparative cycle threshold (Ct) method was used to calculate the relative target gene expression by applying the $2^{(-\Delta\Delta CT)}$ method (Livak and Schmittgen, 2001).

Data Analysis

Behavioral data were analyzed by two-way ANOVA followed by *post hoc* of Newman-keuls. Genotype ($SERT^{+/+}$ vs. $SERT^{+/-}$) and manipulation (naïve vs. TS) were assessed as independent variables. The level of significance was set at $P < 0.05$. For the molecular data two-way ANOVA followed by *post hoc* of Fisher's protected least significant difference (PLSD) was used. Benjamini–Hochberg multiple testing corrections for false discovery rate (FDR) was applied and the significance was set to FDR adjusted p-value < 0.05. All statistical analyses were performed using the Statistics Software version 13.3 (Tulsa, OK, USA) and the graphs were made by GraphPad Prism version 7. Data are presented as means ± standard error (SEM). In the graphs of the molecular data, the group of naïve $SERT^{+/+}$ is set at 100%.

RESULTS

Behavioral Tests

Social Interaction Test

Our main readout in the social interaction test was the time spent on social interaction. For this parameter, we found a significant effect of TS ($F_{(1,30)} = 10.16$; $p = 0.003$). After *post hoc* testing, we found that naïve $SERT^{+/-}$ rats spent less time on social contact ($p = 0.014$) compared to naïve $SERT^{+/+}$ rats while in TS $SERT^{+/-}$ rats this parameter was increased ($p = 0.001$) compared to naïve $SERT^{+/-}$ rats (**Figure 2A**).

For non-social behavior a significant interaction between genotype and TS ($F_{(1,30)} = 15.47$; $p = 0.0005$) was found. *Post hoc* testing showed that naïve $SERT^{+/-}$ rats spent more time on non-social contact ($p = 0.0002$) compared to naïve $SERT^{+/+}$ rats, while TS $SERT^{+/-}$ rats spent less time on non-social behavior ($p = 0.0001$) compared to naïve $SERT^{+/-}$ rats (**Figure 2D**).

For social interest and passive undergoing behavior, we did not find any difference between groups (**Figures 2B,C**).

Elevated Plus-Maze Test

The standard readouts for anxiety as measured in the elevated plus-maze test involve the percentage time spent on the open arms and the percentage of entries onto the open arms. As shown in **Figure 3A**, two-way ANOVA showed that there was a significant interaction between genotype and TS ($F_{(1,30)} = 9.29$; $p = 0.004$) for the mean percentage of open arms time. *Post hoc* testing revealed that naïve $SERT^{+/-}$ animals remained less time on the open arms compared to naïve $SERT^{+/+}$ rats ($p = 0.012$) and TS $SERT^{+/-}$ rats ($p = 0.016$; **Figure 3A**). For the relative number of open arm entries, a significant effect of genotype ($F_{(1,30)} = 5.45$; $p = 0.026$) and an interaction between genotype and TS ($F_{(1,30)} = 6.05$; $p = 0.020$) was observed. In particular, naïve $SERT^{+/-}$animals showed fewer entries on to the open arm compared to naïve $SERT^{+/+}$($p = 0.010$) and TS $SERT^{+/-}$ rats ($p = 0.049$; **Figure 3B**). These data show that TS ameliorated the anxiety observed in naïve $SERT^{+/-}$ rats.

Regarding the time spent on closed arms, no statistical differences were observed (**Figure 3C**). For total time traveled, also no significant genotype or TS manipulation effect was found. The latter confirms that the differences seen in anxiety were not due to differences in locomotor behavior (**Figure 3D**).

Sucrose Consumption Test

As shown in **Figure 4A**, there was a significant effect of genotype ($F_{(1,30)} = 8.19$; $p = 0.007$) for sucrose preference over 5 h. Naïve $SERT^{+/-}$ rats showed a reduction in sucrose preference after 5 h of exposure to the water and sucrose solutions (−25%; $p = 0.049$; Newman-Keuls) compared to the naïve $SERT^{+/+}$ group. After 24 h of exposure, TS $SERT^{+/-}$ rats increased their sucrose preference (+5%; $p = 0.034$) compared to naïve $SERT^{+/-}$rats.

Figure 4B illustrates the sucrose intake data. We found a significant interaction between genotype and TS ($F_{(1,30)} = 6.29$; $p = 0.018$) effect over 2 h. A *post hoc* test revealed a trend towards a reduction (−58%; $p = 0.053$) in sucrose intake in naïve $SERT^{+/-}$ rats after 2 h of exposure compared to naïve $SERT^{+/+}$ rats, while TS $SERT^{+/-}$ rats increased the sucrose intake after 2 h (+177%; $p = 0.016$) compared to naïve $SERT^{+/-}$ rats.

Furthermore, for sucrose intake over 5 h, there was a TS effect ($F_{(1,30)} = 6.24$ $p = 0.018$). *Post hoc* testing showed that the sucrose intake in naïve $SERT^{+/-}$ rats were lower than in naïve $SERT^{+/+}$ rats (−36%; $p = 0.048$) while TS $SERT^{+/-}$ rats showed an increase in sucrose intake after 5 h (+148%; $p = 0.036$) compared to naïve $SERT^{+/-}$ rats. After 24 h of exposure, no significant differences were found in the sucrose intake.

Molecular Results

Bdnf mRNA Expression Levels in the Basolateral Amygdala

We initially investigated total Bdnf mRNA levels in the basolateral amygdala of naïve or TS $SERT^{+/-}$ and $SERT^{+/+}$ animals. We found a significant effect of TS ($F_{(1,31)} = 6.053$, $p = 0.020$) on total Bdnf mRNA levels. *Post hoc* analysis showed that the TS $SERT^{+/+}$ group had a significant decrease of Bdnf mRNA levels compared to the naïve $SERT^{+/+}$ group (−44%, $p = 0.025$; **Figure 5A**).

Based on this result, we decided to evaluate if TS could affect the expression of major Bdnf transcripts. In particular, we quantified the expression levels of the long 3'UTR Bdnf transcripts, associated with dendritic targeting of specific neurotrophin transcripts. Additionally, we measured Bdnf

TABLE 1 | (a) Sequences of primers, reverse primers, and probes used in real-time polymerase chain reaction (RT-PCR) analyses and purchased from Eurofins MWG-Operon.

(a) Gene	Forward primer	Reverse primer	Probe
Total Bdnf	AAGTCTGCATTACATTCCTCGA	GTTTTCTGAAAGAGGGACAGTTTAT	TGTGGTTTGTTGCCGTTGCCAAG
Nr3c1	GAAAAGCCATCGTCAAAAGGG	TGGAAGCAGTAGGTAAGGAGA	AGCTTTGTCAGTTGGTAAAACCGTTGC
Nr3c2	TCGCTTTGAGTTGGAGATCG	ACGAATTGAAGGCTGATCTGG	AGTCTGCCATGTATGAACTGTGCCA
Pvalb	CTGGACAAAGACAAAAGTGGC	GACAAGTCTCTGGCATCTGAG	CCTTCAGAATGGACCCCAGCTCA
Vgat	ACGACAAACCCAAGATCACG	GTAGACCCAGCACGAACATG	TTCCAGCCCGCTTCCCACG
Gad67	ATACTTGGTGTGGCGTAGC	AGGAAAGCAGGTTCTTGGAG	AAAACTGGGCCTGAAGATCTGTGGT
Vglut	ACTGCCTCACCTTGTCATG	GTAGCTTCCATCCCGAAACC	CTTTCGCACATTGGTCGTGGACATT
Fkbp5	GAACCCAATGCTGAGCTTATG	ATGTACTTGCCTCCCTTGAAG	TGTCCATCTCCCAGGATTCTTTGGC
36b4	TTCCCACTGGCTGAAAAGGT AAGGCCTTCCTGGCCGATCCATC	CGCAGCCGCAAATGC	
(b) Gene	**Accession number**	**Assay ID**	
Bdnf long 3' UTR	EF125675	Rn02531967_s1	
Bdnf isoform IV	EF125679	Rn01484927_m1	
Bdnf isoform VI	EF125680	Rn01484928_m1	
Gadd45β	BC085337.1	Rn01452530_g1	
Nr4a1	BC097313.1	Rn01533237_m1	

(b) Probes purchased from Life Technologies which did not disclose the sequence.

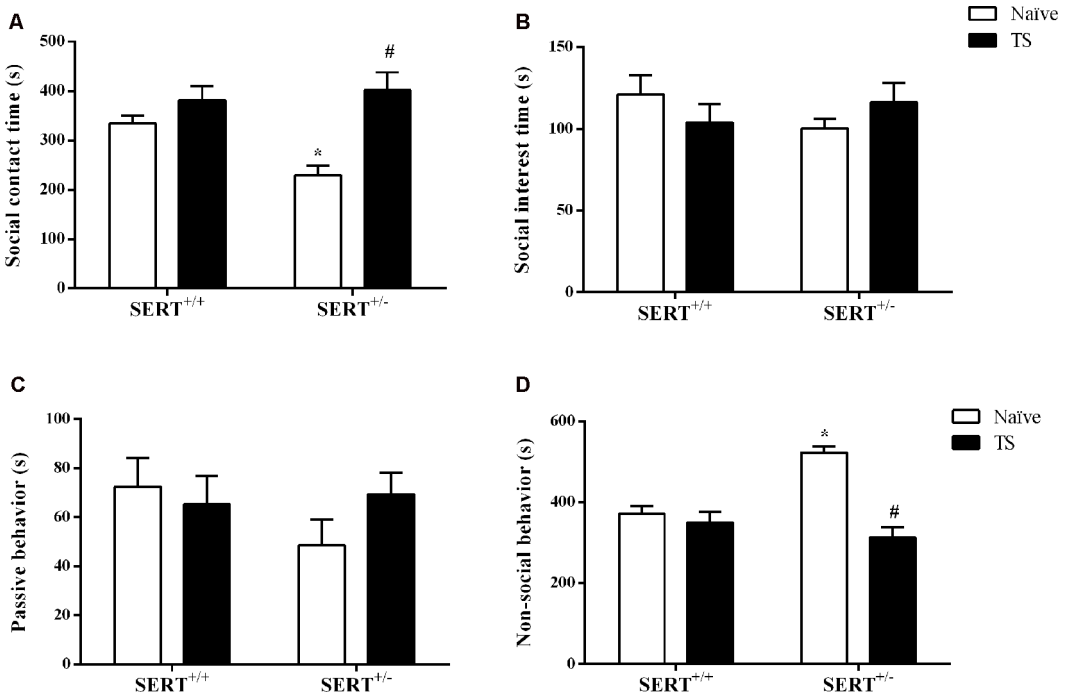

FIGURE 2 | Social interaction test. The time spent on social contact **(A)**, social interest **(B)**, passive behavior **(C)** and non-social behavior **(D)** of heterozygous serotonin transporter knockout (SERT$^{+/-}$) and wild-type (SERT$^{+/+}$) male rats daily exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are represented as mean ± SEM. *Significantly different from naïve SERT$^{+/+}$ rats, $^{\#}$significantly different from naïve SERT$^{+/-}$ rats ($p < 0.05$).

isoforms IV and VI. While isoform IV is localized in the soma, is an indication of altered neuronal activity (Pattabiraman et al., 2005), isoform VI is targeted to dendrites (Chiaruttini et al., 2008). Changes in isoform IV and VI have been associated with mood disorders (Molteni et al., 2010).

No significant differences were found for long 3'UTR Bdnf mRNA levels, indicating that there was no modulation of this pool of transcript on total Bdnf mRNA levels (**Figure 5B**). Two-way ANOVA revealed a significant effect of TS ($F_{(1,31)} = 4.484$, $p = 0.043$) for Bdnf isoform IV, with its mRNA levels being decreased in TS SERT$^{+/+}$ animals (−54% vs. naïve SERT$^{+/+}$, $p = 0.024$, Fisher PLSD) in comparison to the naïve counterpart (**Figure 5C**).

Regarding Bdnf exon VI, two-way ANOVA showed a similar result with a trend in the TS group ($F_{(1,31)} = 3.794$, $p = 0.062$). Indeed, we observed a decrease in Bdnf isoform VI levels in the TS SERT$^{+/+}$ group (−44% vs. naïve SERT$^{+/+}$, $p = 0.035$, Fisher PLSD; **Figure 5D**).

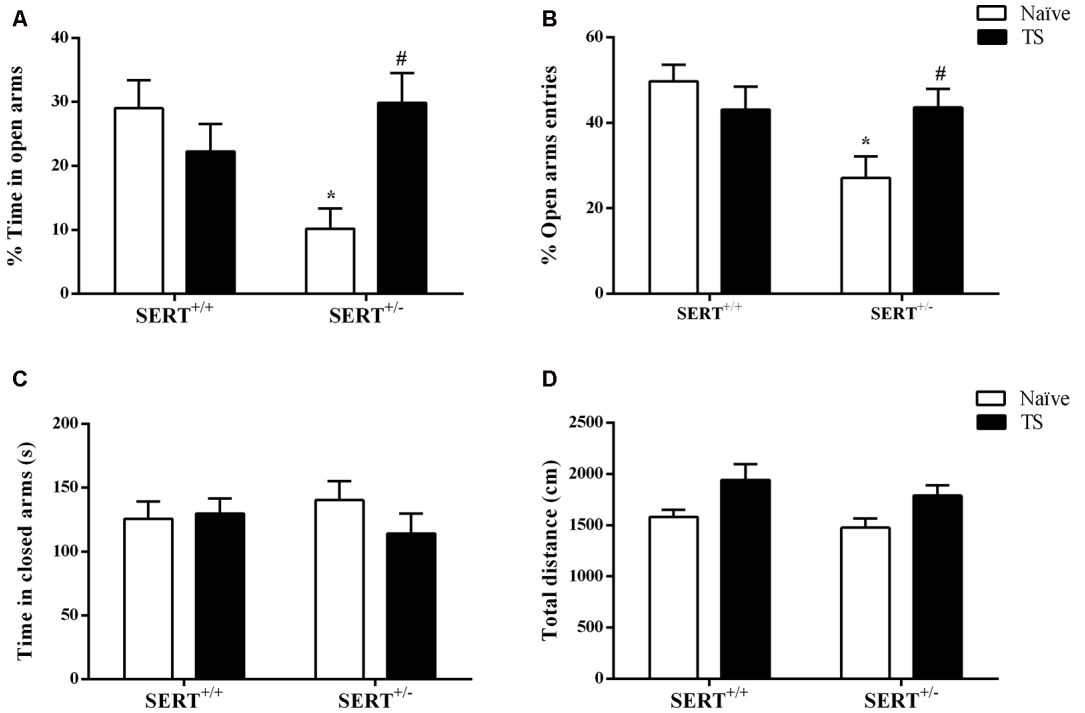

FIGURE 3 | Elevated plus maze test. The mean time of spent in open arms (%; **A**), the mean of entries number in open arms (%; **B**), time spent in closed arms (s; **C**) and total distance traveled (cm; **D**) of heterozygous serotonin transporter knockout ($SERT^{+/-}$) and wild-type ($SERT^{+/+}$) male rats daily exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are represented as mean ± SEM. *Significantly different from naïve $SERT^{+/+}$ rats, #significantly different from naïve $SERT^{+/-}$ rats ($p < 0.05$).

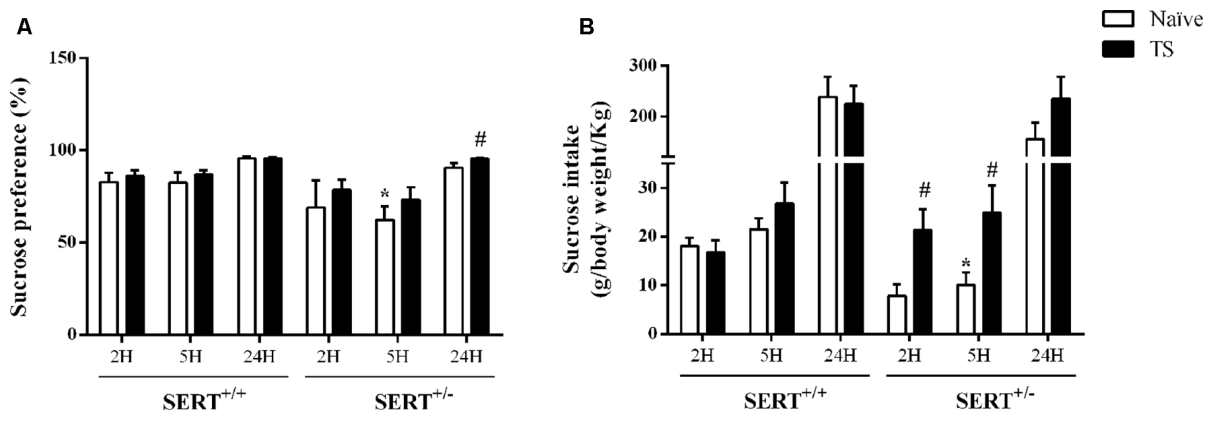

FIGURE 4 | Sucrose consumption test. Sucrose preference **(A)** and sucrose intake **(B)** in heterozygous serotonin transporter knockout ($SERT^{+/-}$) and wild-type ($SERT^{+/+}$) male rats daily exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are represented as mean ± SEM. *Significantly different from naïve $SERT^{+/+}$ rats, #significantly different from naïve $SERT^{+/-}$ rats ($p < 0.05$).

Mineralocorticoid and Glucocorticoid Receptor mRNA Expression Levels in the Basolateral Amygdala

We next investigated if mRNA expression levels of both corticosterone receptors, Nr3c1, and Nr3c2 could be affected by the SERT genotype or TS. Furthermore, the expression of glucocorticoid-responsive genes, including Nr4a1, Gadd45β, and the co-chaperone Fkbp5 were measured in the basolateral amygdala.

Two-way ANOVA showed that TS significantly affected mRNA levels of Nr3c2 ($F_{(1,32)} = 11.243$, $p = 0.002$; **Figure 6B**). We observed that TS induced an increase of its mRNA levels specifically in $SERT^{+/-}$ rats (+42% vs. naïve $SERT^{+/-}$, $p = 0.003$). We did not observe any change in Nr3c1 gene expression

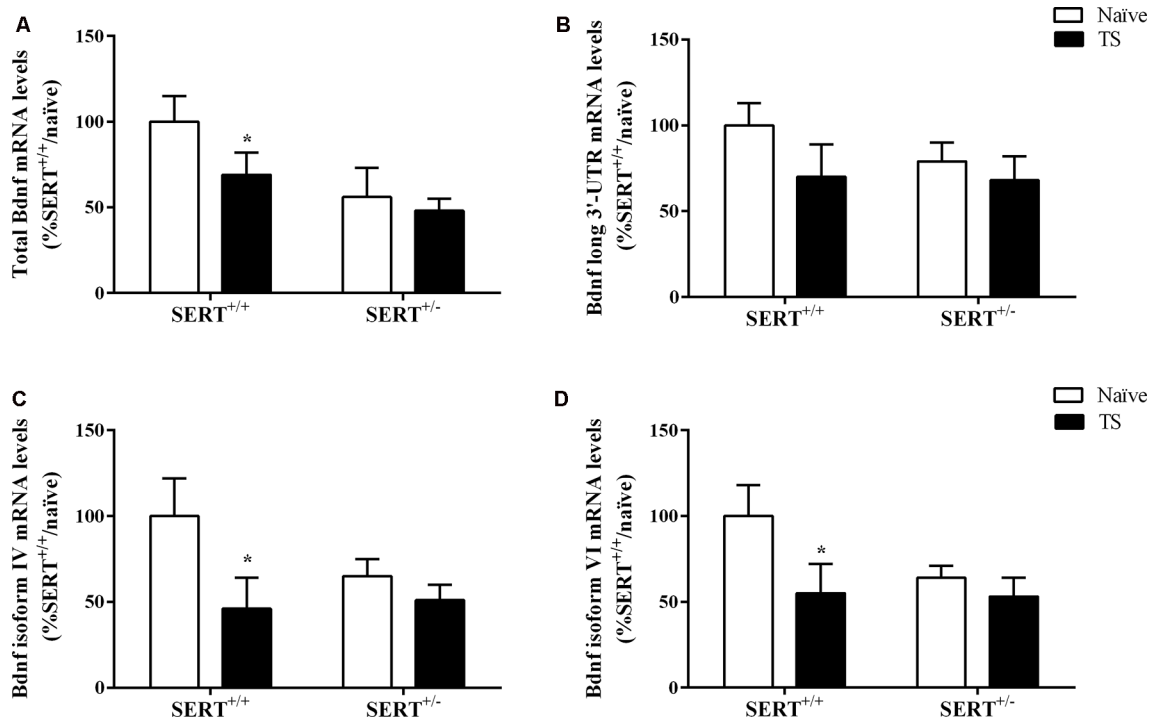

FIGURE 5 | Total Bdnf **(A)**, Bdnf long 3'-UTR **(B)**, Bdnf exon IV **(C)** and exon VI **(D)** mRNA levels in the basolateral amygdala of heterozygous serotonin transporter knockout ($SERT^{+/-}$), and wild-type ($SERT^{+/+}$) male rats daily exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are expressed as a percentage of naïve $SERT^{+/+}$ rats (set at 100%) and are presented as mean ± SEM. *Significantly different from naïve $SERT^{+/+}$ rats ($p < 0.05$).

(**Figure 6A**). As a consequence, the Nr3c1/Nr3c2 ratio was significantly affected by TS ($F_{(1,32)} = 11.541$, $p = 0.014$). Fisher PLSD showed a decrease in this ratio in TS $SERT^{+/+}$ rats compared to their naïve counterparts (−32% vs. naïve $SERT^{+/+}$, $p = 0.002$; **Figure 6C**).

Two-way ANOVA of Nr4a1 mRNA levels revealed a significant effect of TS ($F_{(1,33)} = 13.460$, $p = 0.0009$; **Figure 7A**). *Post hoc* testing revealed a decrease in Nr4a1 mRNA levels both in TS $SERT^{+/+}$ (−34%, $p = 0.005$) and TS $SERT^{+/-}$ rats (−32%, $p = 0.0008$) compared to their naïve counterparts.

Gadd45β gene expression was significantly affected by TS ($F_{(1,33)} = 4.887$, $p = 0.034$, two-way ANOVA) and we found that TS induced a significant reduction of its mRNA levels in TS $SERT^{+/+}$rats compared to naïve $SERT^{+/-}$ rats (−28% vs. naïve $SERT^{+/+}$, $p = 0.009$, Fisher PLSD; **Figure 7B**).

As shown in **Figure 7C**, we found a significant effect of TS on Fkbp5 gene expression ($F_{(1,33)} = 10.377$, $p = 0.003$, two-way ANOVA). Accordingly, we observed a significant increase in Fkbp5 mRNA levels due to TS in $SERT^{+/+}$ rats compared to naïve $SERT^{+/+}$ rats (+39% vs. naïve $SERT^{+/+}$, $p = 0.013$, Fisher PLSD).

mRNA Expression Levels of Key Elements of the GABAergic and Glutamatergic Systems in the Basolateral Amygdala

Finally, we investigated the expression levels of genes encoding key elements of the GABAergic synapses, which are the GABA-producing enzyme (Gad67), vesicular GABA transporter (Vgat), and parvalbumin (Pvalb). Additionally, we measured one glutamatergic marker, vesicular glutamate transporter (Vglut), in the basolateral amygdala.

Two-way ANOVA showed a significant effect of genotype ($F_{(1,33)} = 17.158$, $p = 0.000$) and an interaction between genotype × TS ($F_{(1,33)} = 4.971$, $p = 0.033$) for Gad67 gene expression (**Figure 8A**). We found a significant increase in its mRNA levels specifically in TS $SERT^{+/+}$ animals in comparison to naïve $SERT^{+/+}$ rats (+30%, $p = 0.007$, Fisher PLSD). We did not observe any alteration in Pvalb mRNA levels and Vgat mRNA levels (**Figures 8B,C**).

As shown in **Figure 9A**, we observed a significant effect of TS on Vglut gene expression ($F_{(1,33)} = 7.071$, $p = 0.015$, two-way ANOVA). TS $SERT^{+/+}$ animals showed a decrease in its mRNA levels (−47% vs. naïve $SERT^{+/+}$, $p = 0.009$, Fisher PLSD).

Finally, we calculated the Vglut/Vgat ratio. Two-way ANOVA revealed that there was a trend effect for TS on this ratio ($F_{(1,32)} = 3.812$, $p = 0.061$). Further, *post hoc* testing revealed that the ratio was significantly reduced in TS $SERT^{+/+}$ rats compared to naïve $SERT^{+/+}$ rats (−55%, $p = 0.047$, Fisher PLSD; **Figure 9B**).

DISCUSSION

In this study, we investigated the effect of neonatal TS in male $SERT^{+/-}$ rats on social and affective behavior, as well

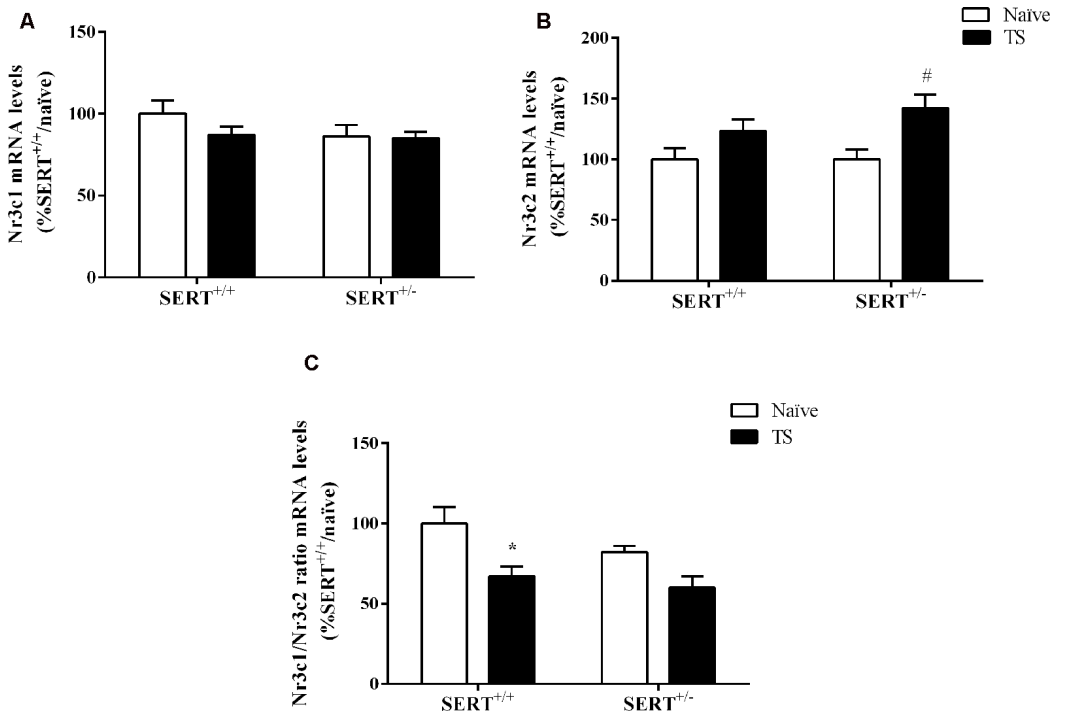

FIGURE 6 | Glucocorticoid receptor (Nr3c1) **(A)**, mineralocorticoid receptor (Nr3c2) **(B)**, and the ratio between Nr3c1 and Nr3c2 **(C)** mRNA levels in the basolateral amygdala of heterozygous serotonin transporter knockout ($SERT^{+/-}$), and wild-type ($SERT^{+/+}$) male rats daily exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are expressed as a percentage of naïve SERT naïve rats (set at 100%) and are presented as mean ± SEM. *Significantly different from naïve $SERT^{+/+}$ rats, #significantly different from naïve $SERT^{+/-}$ rats ($p < 0.05$).

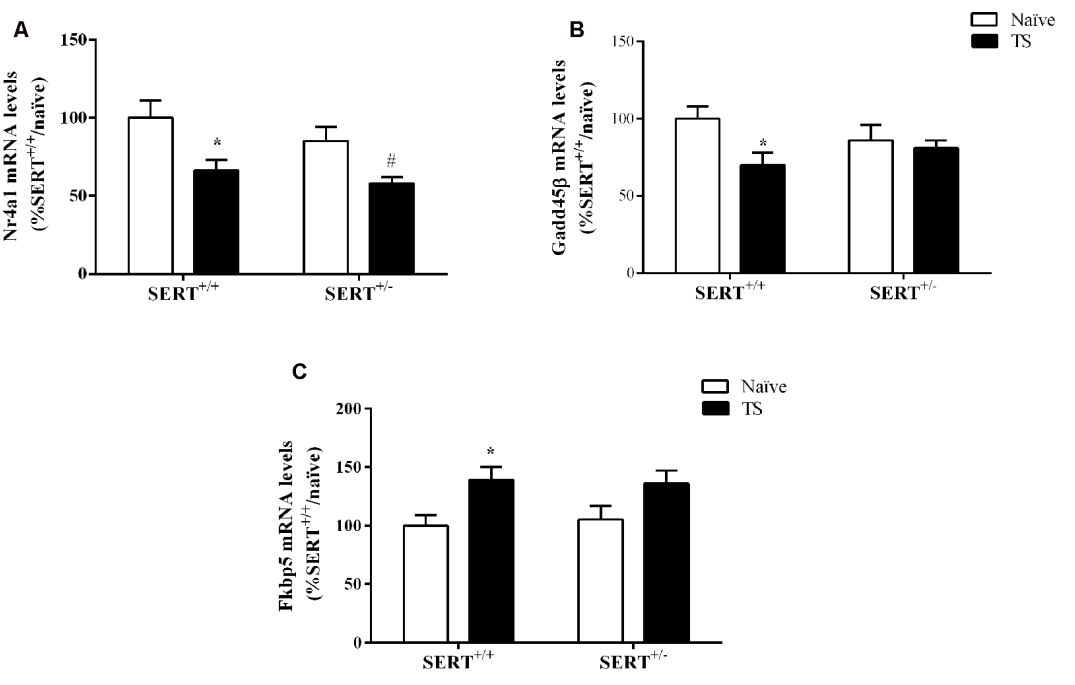

FIGURE 7 | Nr4a1**(A)**, Gadd45β **(B)** and Fkbp5 **(C)** mRNA levels in the basolateral amygdala of heterozygous serotonin transporter knockout ($SERT^{+/-}$), and wild-type ($SERT^{+/+}$) male rats daily exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are expressed as a percentage of naïve $SERT^{+/+}$ rats (set at 100%) and are presented as mean ± SEM. *Significantly different from naïve $SERT^{+/+}$ rats, #significantly different from naïve $SERT^{+/-}$ rats ($p < 0.05$).

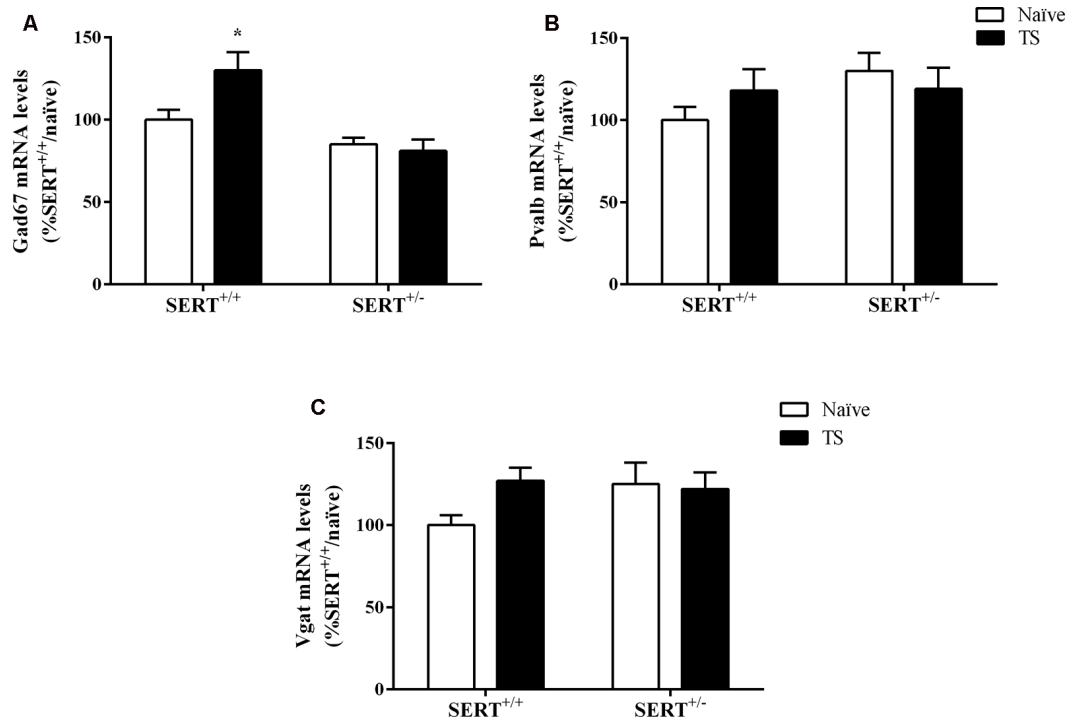

FIGURE 8 | Gad67 **(A)**, Parvalbumin (Pvalb; **B**) and vesicular GABA transporter (Vgat; **C**) mRNA levels in the basolateral amygdala of heterozygous serotonin transporter knockout ($SERT^{+/-}$) and wild-type ($SERT^{+/+}$) male rats exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are expressed as a percentage of naïve $SERT^{+/+}$ (set at 100%) and are represented as mean ± SEM. *Significantly different from naïve $SERT^{+/+}$ rats ($p < 0.05$).

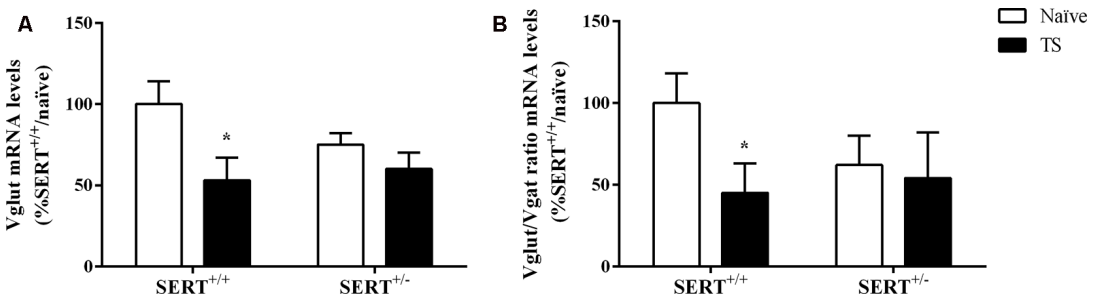

FIGURE 9 | Vesicular glutamate transporter (Vglut; **A**) and the ratio between Vglut and vesicular GABA transporter (Vgat; **B**) mRNA levels in the basolateral amygdala of heterozygous serotonin transporter knockout ($SERT^{+/-}$) and wild-type ($SERT^{+/+}$) male rats exposed to TS from postnatal day 8–14 or a control treatment (no TS-naïve). Data are expressed as a percentage of naïve $SERT^{+/+}$ (set at 100%) and are represented as mean ± SEM. *Significantly different from naïve $SERT^{+/+}$ rats ($p < 0.05$).

as gene expression in the basolateral amygdala as readouts. By applying TS 1 × day/10 min from PND 8–14 we observed that diminished social contact and increased non-social behavior in naïve $SERT^{+/-}$ rats were normalized in TS $SERT^{+/-}$ animals. Also, we observed that increased anxiety as measured in the elevated plus-maze test and reduced anhedonia as measured in the 3% sucrose consumption test was normalized in TS $SERT^{+/-}$ rats, suggesting that neonatal TS had a beneficial influence on the development of the effective behavior in $SERT^{+/-}$animals. Interestingly, at the molecular level, we observed a strong effect of TS on mRNA expression levels of genes encoding key elements of the Bdnf, GABA and glutamate systems, and on mRNA expression levels of genes encoding glucocorticoid-responsive genes in the basolateral amygdala of $SERT^{+/+}$ but not $SERT^{+/-}$ animals.

Previous work has demonstrated that inherited down-regulation of SERT is associated with increased sensitivity to the adverse effects of early life stress, resulting in increased anxiety- and depression-like behavior (Houwing et al., 2019). However, the SERT does not only increase sensitivity to negative environmental stimuli, since this would preclude the existence of the high frequency of the 5-HTTLPR in the human

population. Given that, it is unlikely that a so common gene variance is maintained throughout evolution only exerting negative effects. Indeed, there is evidence, particularly from human studies, that the 5-HTTLPR also increases sensitivity to positive environmental stimuli, in line with the differential susceptibility theory (Belsky et al., 2009). TS is a positive manipulation that when applied during neonatal periods can prevent the development of anxiety and depression (Boufleur et al., 2012; Freitas et al., 2015). Accordingly, we observed that naïve SERT$^{+/-}$ rats displayed increased anxiety in the elevated plus-maze test and that this behavior was normalized in TS SERT$^{+/-}$ rats. Also, we observed a reduction in sucrose preference and intake in naïve SERT$^{+/-}$ animals in the sucrose 3% preference test, indicative of an anhedonic state in the animals, while TS SERT$^{+/-}$ animals showed a normalization of the sucrose preference up to the level of SERT$^{+/+}$ rats. Based on these findings we can hypothesize that animals submitted to TS did not develop the anxiety- and anhedonia-like behaviors as observed in naïve SERT$^{+/-}$ animals. Since we did not test the influence of negative stimuli on SERT$^{+/-}$ rats, our findings would reflect vantage sensitivity, which reflects a disproportionally increased sensitivity to positive stimuli (Pluess and Belsky, 2013).

According to literature, SERT$^{+/-}$ animals present an increase in social avoidance after stress exposure (Bartolomucci et al., 2010). Here, naïve SERT$^{+/-}$ animals showed a reduction in social contact time and an increase in non-social behavior time, while TS normalized these observations in SERT$^{+/-}$ animals. Sociability has been strongly associated with amygdala function (Hitti and Siegelbaum, 2014) since the neuroplastic changes accompanying the social decisions in rodents involves modulation of the amygdala. For instance, amygdala lesions have been related to alterations in social behavior in juvenile and adult rats (Daenen et al., 2002) and changes in amygdala circuits also have been associated with sociability deficits and anxiety symptoms in mice (Li et al., 2019).

At the molecular level, in general, we did not find significant alterations in naïve SERT$^{+/-}$ rats compared to naïve SERT$^{+/+}$ rats, while in TS SERT$^{+/+}$ animals there were basolateral amygdala modifications when compared to naïve SERT$^{+/+}$ animals. Possibly, SERT$^{+/+}$ animals exhibit a large dynamic space for adjustments to buffer environment influences while SERT$^{+/-}$ animals may lack such a dynamic space because of a tonic elevation in neuronal activity. This may render them susceptible to environmental influences, including supportive stimuli (Homberg et al., 2016). A previous study reported that in SERT$^{-/-}$ mice, compared to wild-type mice, spine density in the amygdala was significantly increased. Interestingly, after stress exposure, behavioral changes were observed selectively in the SERT$^{-/-}$ mice, while spine density remained unaltered in these mice. In wild-type controls, spine density increased up to the level of that of SERT$^{-/-}$ mice. These findings suggest that a tonic increase in excitability reduces plasticity when a further increase in excitability is required to process the stress, failing to buffer the effects of stress and exaggerated behavioral stress response (Nietzer et al., 2011). It is plausible that a comparable mechanism is at play in the present study, with SERT$^{+/-}$ rats responding behaviorally to TS due to a lack of a dynamic range to molecularly "neutralize" the effects of TS.

Previous works demonstrated that Bdnf levels were reduced in the prefrontal cortex and hippocampus of SERT$^{-/-}$ animals throughout life (Molteni et al., 2010; Calabrese et al., 2013). Bdnf is a key player in neurodevelopment and neuronal plasticity. Here, we observed a decrease in the expression of total Bdnf and its isoform IV and VI in TS SERT$^{+/+}$ animals compared to naïve SERT$^{+/+}$ rats. Although an increase in Bdnf expression in the brain is generally related to an antidepressant effect, Bdnf has been reported to have an opposite role in the amygdala. Indeed, overexpression of Bdnf in the amygdala has been related to an anxiogenic response (Govindarajan et al., 2006). Also, a Bdnf up-regulation in the central amygdala of SERT$^{-/-}$ rats is related to enhance negative emotional state, contributing to a compulsive drug self-administration behavior (Caffino et al., 2019). Not only the total Bdnf but also alterations in Bdnf isoform VI and IV were related to increased anxiety in male rats after acute stress exposure (Luoni et al., 2016; Pandey et al., 2017). Although a previous study demonstrated that TS in Wistar rats led to an increase in Bdnf levels in the hippocampus, along with a beneficial effect on anxiety and an improvement in working memory as evaluated using the Y-maze test (Antoniazzi et al., 2017), in our study the decrease of Bdnf expression in the basolateral amygdala in TS animals could be indicative of a protective mechanism against anxiety and anhedonic behaviors.

To assess if the HPA axis is modulated by TS in SERT animals, we investigated the expression of both glucocorticoid (Nr3c1) and mineralocorticoid (Nr3c2) receptor encoding genes. There was an increase in Nr3c2 gene expression only in TS SERT$^{+/-}$ animals compared to TS SERT$^{+/+}$ animals and there were no changes in Nr3c1 gene expression. Nonetheless, the ratio of Nr3c1/Nr3c2 was found to be increased in the basolateral amygdala of both SERT$^{+/+}$ and SERT$^{+/-}$ TS exposed animals. In previous work, this ratio was found to be reduced in the paraventricular nucleus and hippocampus of stressed animals (Brydges et al., 2014; Murgatroyd et al., 2015). The ratio between glucocorticoid and mineralocorticoid expression plays a key role in the promotion of health, homeostasis, and adaptation (de Kloet et al., 1993). An increase in this ratio as observed in TS SERT$^{+/-}$ animals could indicate a change in homeostasis, leading to neuroadaptation and improving the ability to cope with different environmental situations and explaining the normalization of anxiety behavior observed in this group. Furthermore, we measured expression levels of glucocorticoid-regulator FK506-binding protein 51 (Fkbp5), Nr4a1, and growth arrest and DNA damage-inducible factor 45 (Gadd45β). We observed that FKBP5 was increased in TS SERT$^{+/+}$ animals compared to naïve SERT$^{+/+}$. Literature is controversial regarding Fkbp5 expression in the brain. Some studies showed increased expression levels of Fkbp5 in the basolateral amygdala of stressed rats (Xu et al., 2017) as well as increased FKBP5 mRNA in the ventral prefrontal cortex of homozygous SERT rats after early life stress exposure (van der Doelen et al., 2014). In contrast, maternal separation reduced Fkbp5 expression in the hippocampus and did not alter in the amygdala of adult male mice (Candemir et al., 2019).

Furthermore, we observed that Nr4a1 expression was reduced in both TS manipulated SERT$^{+/+}$ and SERT$^{+/-}$ animals. Nr4a1 is an activity-dependent immediate early-gene responding to a variety of sensory stimuli, adapting the synaptic activity in response to stimuli. Prolonged expression of Nr4a1 can lead to mitochondrial malfunction and altered synaptic plasticity (Chen et al., 2014; Jeanneteau et al., 2018). Accordingly, the reduction of Nr4a1 expression in TS groups could explain the mechanism of protection against brain disturbances. Moreover, Gadd45β has been associated with amygdala-related learning tasks and the epigenetic programming of social behavior (Kigar et al., 2015). Despite Gadd45β's effects on social behavioral function, we did not observe a change in Gadd45β expression in both naïve and TS SERT$^{+/-}$ animals. Only in TS SERT$^{+/+}$ animals, we found a change, possibly contributing to the maintenance of brain homeostasis. This could explain why there was no change in behavior, as a response to TS in SERT$^{+/+}$ rats.

The basolateral amygdala is a brain region involved in the processing of emotional signals and contains GABAergic interneurons. The amygdala undergoes developmental changes in early life and is fully mature around adolescence. Environmental events during early life or the developmental stage of the amygdala can have long-lasting persisting effects (Bessières et al., 2019). The balance between inhibitory and excitatory neurotransmission is necessary for brain development (Chamberland and Topolnik, 2012). Here, we investigated the expression levels of Gad67, Pvalb, vesicular GABA transporter (Vgat), and vesicular glutamate transporter (Vglut) to reflect the excitatory/inhibitory balance in the basolateral amygdala. We observed an increase in the GABAergic marker Gad67 in TS SERT$^{+/+}$ rats compared to naïve SERT$^{+/+}$ rats. Gad67 serves as an inhibitory marker that helps in the GABA synthesis under basal conditions. Stress is related to decreases in Gad67 expression in the medial prefrontal cortex, impairing social behavior in rats, and reducing inhibitory synapses in the brain (Ohta et al., 2019). Evidence has shown that treatment with the antidepressant duloxetine can restore the reduction of Gad67 in stress-depressive state animals (Guidotti et al., 2012). Moreover, inhibitory and excitatory amygdaloid circuits were found to be affected in patients with depression, bipolar disorder, or schizophrenia, which was paralleled by a decrease in GAD67 and an increase in VGLUT levels in various nuclei of the amygdala in all patients (Varea et al., 2012). The increase in Gad67 observed in TS SERT$^{+/+}$ rats may suggest that the manipulation increased the number of GABAergic terminals in the basolateral amygdala, preventing anxious-depressive behaviors. Regarding excitatory neurotransmission, TS SERT$^{+/+}$ animals showed a reduction in both Vglut expression levels and Vglut/Vgat ratio. Stress has been associated with enhancement of glutamatergic neurotransmission in prefrontal cortex and amygdala, and peripubertal stress has been related to increasing the Vglut/Vgat ratio, which in turn was associated with the development of psychiatric disorders (Yuen et al., 2011; Tzanoulinou et al., 2014). Although we did not find alterations in SERT$^{+/-}$ groups, the maintenance of normal anxiety behavior observed in TS SERT$^{+/+}$ animals could be explained by the reduction in this glutamatergic expression, in which these reduced levels could prevent sensitivity to adversity in these animals.

Summarized, our findings indicate that exposure to neonatal TS in SERT$^{+/-}$ and SERT$^{+/+}$ animals result in lasting changes in emotional and social parameters and molecular changes in the basolateral amygdala. Generally, the data suggest that TS in SERT$^{+/-}$ animals had pronounced effects on anxiety and social behaviors, but not on gene expression in the basolateral amygdala, possibly because of SERT$^{+/-}$ animals present at baseline a tonic elevation in neuronal activity, hindering further changes in gene expression upon environmental challenges. On the other hand, TS in SERT$^{+/+}$ animals altered molecular parameters in the basolateral amygdala but these effects were not accompanied by behavioral changes, suggesting that SERT$^{+/+}$ animals might have a greater dynamic range for adjustments, allowing them to remain unaffected by TS. One limitation of the present study is that we did not include female rats. Since women show more susceptibility to depression (Kuehner, 2017), studies comparing male and female are still needed to better understand the relation between TS and SERT$^{+/-}$ animals in both sexes. To conclude, this is the first study to investigate the beneficial effects of an early-life supportive environmental stimulus on later life behavior of stress-sensitive SERT$^{+/-}$ animals, with results that will further our understanding of how a supportive environment particularly benefits vulnerable individuals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Committee for Animal Experiments of the Radboud University Nijmegen, The Netherlands.

AUTHOR CONTRIBUTIONS

KR and CB experimented and collected the behavioral data. CB, FC, and PB performed and analyzed the molecular data. KR analyzed the data and wrote the manuscript. JH, MV, CA, MB, and KR designed the study and interpreted the data. JH, MV, and MB reviewed and edited the manuscript. JH and MR were responsible for the funding acquisition. All authors contributed to the article and approved the submitted version.

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Sleep Quality as a Mediator in the Relationship Between Perceived Stress and Job Burnout Among Chinese Nurses: A Structural Equation Modeling Analysis

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Background: Job burnout has become an increasing prevailing phenomenon among nurses in both developed and developing countries. There is a paucity of research exploring the relationship between perceived stress (i.e., the level of one's perception or appraisal of stress rather than objective stressful events) and job burnout and no existing literature examining the mediating role of sleep quality in the relationship between these two constructs. The objective of the study was to examine if sleep quality mediates the relationship between perceived stress and job burnout.

Methods: Cross-sectional data were collected from a total of 1,013 nurses working in six public tertiary hospitals in China. The self-administered questionnaire included demographic information, the Maslach Burnout Inventory-General Scale, the Pittsburgh Sleep Quality Index and the Perceived Stress Scale. Hierarchical multiple regression (HMR) analyses were performed to examine the contribution of each covariate to the prediction of job burnout. Structural equation modeling (SEM) was employed to test whether the proposed relationships between variables involved existed.

Results: Both perceived stress and poor sleep quality exhibited strong positive associations with job burnout among Chinese nurses. The SEM analysis confirmed the direct pathway from perceived stress to burnout and the indirect pathway mediated by sleep quality. The direct effect of perceived stress on job burnout was found to be statistically significant and positive ($\beta = 0.69$, $p < 0.05$). There existed statistically significant effects of sleep quality on both perceived stress ($\beta = 0.48$) and job burnout ($\beta = 0.29$). The path coefficients of perceived stress on job burnout were significantly reduced ($\beta = 0.56$) when sleep quality was modeled as a mediator. The bias-corrected and accelerated bootstrap test revealed that sleep quality had a significant mediating effect on the relationship between perceived stress and job burnout (a * b = 0.139, BCa 95%, CI: 0.110∼0.174).

Conclusion: Perceived stress might exert significant effects on burnout both directly and indirectly through the mediating role of sleep quality. Efforts to reduce burnout among nurses in clinical settings may benefit from interventions for coping with perceived stress and practices for promoting healthy sleep.

Keywords: burnout, perceived stress, sleep quality, nurses, structural equation modeling

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INTRODUCTION

Job burnout has been recognized as an occupational health problem that occurs during long-term exposure to work-related stress and may involve multiple symptoms (1). Emotional exhaustion, depersonalization, and diminished personal accomplishment are three specific characteristics constituting burnout (2) and World Health Organization has recently classified it as a syndrome "resulting from chronic workplace stress that has not been successfully managed" (3).

Nurses have long been considered as working in a profession where they are confronted with a wide range of stressors including emotionally demanding patient contacts, workload and time pressure (4), ever-changing technology and institutional and ethical challenges (5), and often being confronted with insufficient resources to effectively cope with high job demands (4). Long-term exposure to stress is common in nursing, which may affect up to 71% of nurses (6) and cause mental, physical and emotional exhaustion and subsequently result in burnout (7).

Burnout, though depending on individual peculiarities, can be linked to a wide variety of detrimental personal and organizational outcomes. Nurses have been found to be particularly susceptible to burnout in hospital settings (8). Burnout can manifest in both physical and psychological symptoms including, among others, weakness, insomnia, anxiety, depression, hostility, aggressiveness (9, 10). Burnout can also lead to reduced work effectiveness and job satisfaction (11) and higher levels of absenteeism and turnover among nurses (10). Furthermore, it can result in decline in patient satisfaction and the quality of nursing care (12, 13). Although reports of the rates of burnout among nurses have varied, burnout has become an increasing prevailing phenomenon in different nursing specialties and among nurses in both developed and developing countries. It has been documented that the level of burnout has been increasing steadily over the recent years among Chinese nursing staff (14), affecting up to 68.1% in the existing literature (15).

Recent literature has found sleep quality had an association with the occurrence of burnout syndrome and contributed to nurses' recovery from fatigue and psychological stress caused by work (16). Poor sleep quality may not only result in health problems of the health care personnel but also may be linked to impaired clinical performance and higher risk of medical errors that may jeopardize the safety of patients (17). It has been widely recognized as a critical issue among the nursing staff. It was found that up to 55% of clinical nurses working in general hospitals in Mainland China were susceptible to sleep problems (18). A cross-sectional study conducted among Turkish nurses reported that 79.1% of the participants experienced poor sleep quality and those with poor sleep quality were found to experience more sleepiness at work and have higher levels of burnout (19). Adequate amount of sleep has been found to be a protective factor for burnout, which helps nurses restore energy and recover from the exhaustion of working days (20). In Medscape's newly-released 2020 National Report on physicians' burnout, millennial physicians are most likely to resort to sleep to cope with burnout (21). Longer sleep onset and more fragmented sleep has been associated with greater levels of burnout (22). Short sleep duration was shown to be common among the nursing staff. It has been documented that there was lower likelihood of job strain and burnout for those who slept 7 h or longer every working day (23) and fewer hours slept on average served as a predictor of higher depersonalization (24).

Although studies have yielded results that indicate the association of sleep quality with work-related stress and burnout independently among the nursing staff, there is no existing literature examining whether sleep quality plays a mediating role between stress and burnout. Also, despite that fact that stress has been documented as a predictor of burnout in numerous theoretical and empirical studies, stress propensity varies between individuals and the degree to which stress exerts a negative impact depends on one's perception or appraisal of stress (25). One's response to stressful events (often referred to as stressors) is determined by how he or she perceives or appraises stress rather than the objective occurrence of events (26). Research focusing on the effect of perceived stress (i.e., the level of appraised stress rather than objective stressful events) on burnout is scarce and such research has not yet been conducted among nurses in Chinese clinical settings. In this study, we hypothesized that perceived stress could have positive effect on job burnout and sleep quality could act as a mediator in the relationship between perceived stress and job burnout. Based on the research findings reported above, the objective of the study was to explore: (1) whether a relationship between perceived stress and burnout exists among Chinese nurses; (2) whether sleep quality could act as a mediator in the relationship between perceived stress and job burnout.

MATERIALS AND METHODS

Research Design and Sample Selection

The current study was based on cross-sectional data with propositional sampling collected from October 2017 to February 2018 among 1,300 nurses working in six public tertiary hospitals in Shenyang the capital of Liaoning province, the largest city in northeastern China. Approximately twenty-five percentage of the nurses who work in the clinical departments including medical, surgical, gynecological, pediatric, and other divisions were chosen randomly from each of these six hospitals. Eligibility criteria for the participants include: (1) licensed as a registered nurse; (2) working in a nursing position for more than 1 year; (3) voluntarily participating in the present study. A self-administered questionnaire, which took approximately 25 min to complete, was distributed. A total of sample of 1,013 nurses provided effective responses to the questionnaire and constitute our final participants, which achieved an effective response rate of 77.92%.

Ethics Statement

The study was conducted in accordance with the ethical guidelines and approved by the Committee on Human Experimentation of China Medical University. The study protocol was fully explained and written informed consent was obtained from each participating nurse before the initiation of study procedures. Nurses' participation in the study was

entirely voluntary and anonymous; their personal information and responses were held in strict confidentiality.

Instruments

Demographic characteristics examined in this study included age, gender, marital status, level of education, and monthly income. "Educational level" was categorized as "Junior college or below" and "bachelor or above." "Marital status" was classified as "Married or cohabiting" and "other." "Monthly income" was divided into "<3,000 RMB" and "≥3,000 RMB."

Job burnout was measured with the Maslach Burnout Inventory-General Scale, which is the most widely used measurement tool of burnout (27). It assesses burnout in three subscales; emotional exhaustion, depersonalization, and personal accomplishment. The Chinese version consists of 15 items including five items measuring emotional exhaustion, four items measuring the depersonalization and six items measuring personal accomplishment. Each item is scored on a seven-point frequency scale ranging from 0 ("never") to 6 ("daily"), with higher scores in the subscales of emotional exhaustion and depersonalization and lower scores in the subscale of personal accomplishment indicative of higher levels of burnout. In the present study, the Cronbach's alpha for the scale was 0.899.

Sleep quality was assessed with Chinese version of the Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index is the most commonly used instrument to assess quality of sleep in clinical and research settings (28, 29). It comprises 19 self-rated items measuring sleep quality in seven dimensions including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction (28). Each item is scored on a Likert scale ranging from 0 to 3, indicative of the extent from "no difficulty" to "severe difficulty." A higher global score represents poorer sleep quality. The Chinese version of Pittsburgh Sleep Quality Index has been validated as a highly reliable instrument for measuring the sleep quality among Chinese nurses (16). In the present study, the Cronbach's alpha for the scale was 0.697.

Perception of stress was measured by the Perceived Stress Scale (PSS), which was developed by Cohen (26) and has been extensively used as a classic stress assessment instrument for measuring the perception of stress. The Chinese version of the 10-item Perceived Stress Scale has been shown to have good reliability and validity (30). Items in this scale included "In the last month, how often have you been upset because of something that happened unexpectedly?" and "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?" each of which was reported on a 0–4 scale ranging from "never" to "very often," with higher scores indicative of higher levels of perceived stress. In the present study, the Cronbach's alpha for the scale was 0.808.

Statistical Analysis

The data were analyzed using SPSS version 17.0. The differences in job burnout among categorical groups were examined using *t*-tests and one-way ANOVA. The correlations between three dimensions of job burnout, perceived stress and sleep quality were explored using correlation analysis. Hierarchical multiple regression (HMR) analyses were performed to examine the contribution of each covariate to the prediction of job burnout. Job burnout was used as the dependent variable and the independent variables (i.e., demographic characteristics, perceived stress, and sleep quality) were entered at subsequent steps. The following criteria should be met based on the approach proposed by Baron and Kenny (31) for establishing mediation: (1) the independent variable (perceived stress) is a significant predictor of the dependent variable (job burnout); (2) the independent variable (perceived stress) is a significant predictor of the potential mediator (sleep quality); (3) the potential mediator (sleep quality) is a significant predictor of the dependent variable (job burnout); (4) the effect of the independent variable (perceived stress) on the dependent variable (job burnout) is significantly reduced or no longer statistically significant when the mediator (sleep quality) is introduced. The Sobel test using structural equation modeling (SEM) was conducted to confirm the mediating effect of sleep quality on the relationship between perceived stress and job burnout. The goodness-of-fit index —$\chi 2/df < 5$, GFI, CFI, TLI > 0.90, and RMSEA < 0.08 was considered to indicate an adequate model fit. It could be speculated that sleep quality might have a mediating effect if a decrease in the size of direct path coefficients of perceived stress on job burnout or a disappearance of statistical significance could be observed upon the inclusion of sleep quality as a potential mediator in the model. The bootstrapping strategy was performed to test the mediating effect (a^b product) of sleep quality on the relationship between perceived stress and job burnout (32). The bootstrap estimates were calculated based on 5,000 resamples and 95% bias-corrected and accelerated confidence intervals. Significance of a mediating effect was determined if the value of zero was outside confidence interval. All statistical tests were two-tailed with *P*-values <0.05 being considered statistically significant.

RESULTS

The demographic information of participants and the corresponding distribution of job burnout are shown in **Table 1**. Among the 1,013 nurses, 38 (3.8%) were male and 975 (96.2%) were females. Four hundred and nineteen (41.4%) fell within the <30 age group and (714) 70.5% had bachelor's or higher degrees. Significant differences were observed in scores of job burnout, in particular, the subscale of personal accomplishment, regarding age, gender, marital status, education level and monthly income. Specifically, significantly higher levels of personal accomplishment were also observed in those aged 30 or above, those who are currently not married or cohabiting, those who had bachelor's or higher degree, and those who earned no <3,000 RMB per month ($P < 0.01$).

The correlations between different dimensions of burnout, perceived stress and sleep quality are presented in **Table 2**. The results reveal that significant correlations exist between all three dimensions of burnout and perceived stress ($P < 0.01$) and sleep quality ($P < 0.01$). Specifically, perceived stress

TABLE 1 | Demographic characteristics and the distributions of job burnout among nurses (N = 1,013).

Variables	*N* (%)	EE (Mean ±SD)	DE (Mean±SD)	PA (Mean±SD)
Age (yrs)				
<30	419 (41.4)	11.91 ± 6.68	10.17 ± 6.79	19.76 ± 8.71
≥30	594 (58.6)	12.28 ± 6.80	10.37 ± 7.12	21.86 ± 9.37**
Gender				
Male	38 (3.8)	10.47 ± 6.03	9.92 ± 6.23	17.03 ± 9.70
Female	975 (96.2)	12.19 ± 6.77	10.30 ± 7.01	21.15 ± 9.10**
Marital status				
Married or cohabiting	682 (67.3)	11.80 ± 6.95	10.22 ± 6.91	19.79 ± 8.71
Others	331 (32.7)	12.28 ± 6.65	10.32 ± 7.02	21.57 ± 9.32**
Education				
Junior college and below	299 (29.5)	11.68 ± 6.52	10.03 ± 6.71	19.08 ± 9.74
Bachelor degree and above	714 (70.5)	12.31 ± 6.84	10.40 ± 7.10	21.79 ± 8.78**
Monthly income				
<3,000	281 (27.7)	11.97 ± 6.90	10.60 ± 6.99	19.62 ± 8.88
≥3,000	732 (72.3)	12.19 ± 6.69	10.17 ± 6.98	21.52 ± 9.21**

*Significant at the 0.05 level (two-tailed); **Significant at the 0.01 level (two-tailed). Values are presented as mean ± standard deviation. EE, Emotional exhaustion; DE, Depersonalization; PA, Personal accomplishment.*

TABLE 2 | The effect size of continuous variables.

	1 EE	2 DE	3 PA	4 PS	5 SQ
1 EE	1				
2 DE	0.760**	1			
3 PA	0.132**	0.015	1		
4 PS	0.484**	0.412**	0.271**	1	
5 SQ	0.524**	0.448**	0.088**	0.335**	1

*Significant at the 0.05 level (two-tailed); **Significant at the 0.01 level (two-tailed). EE, Emotional exhaustion; DE, Depersonalization; PA, Personal accomplishment; PS, Perceived stress; SQ, Sleep quality.*

(PS) was positively correlated with emotional exhaustion (EE), depersonalization (DE), and personal accomplishment (PA). Poor sleep quality (SQ) was associated with increased levels of all three dimensions of burnout. As shown in **Table 2**, the effect-sizes of the correlations of Perceived stress with Emotional exhaustion and Depersonalization were above 0.3 respectively, which indicated a medium effect-size with both practical and statistical significance; the effect-size of the correlation between Perceived stress and Personal accomplishment was above 0.1, which was small being statistically significant but practically negligible. Also, the effect-sizes of the correlations of Sleep qualtiy with Emotional exhaustion and Depersonalization were above 0.3 respectively, which indicated a medium effect-size with both practical and statistical significance; the effect-size of the correlation between Sleep quality and Personal accomplishment was above 0.1, which was small being statistically significant but practically negligible. R^2 and adjusted R^2 were included in **Table 3** to better reflect the size-effects of the correlations of Job burnout with Perceived stress and Sleep quality.

As is indicated in **Table 3**, perceived stress was significantly positively correlated with emotional exhaustion, accounting for 23.1% of the variance. Poor sleep quality was also significantly positively correlated with emotional exhaustion, explaining an additional 15% of the variance. The results indicate the potential effect of perceived stress on emotional exhaustion among Chinese nurses might be partially mediated by sleep quality. The regression coefficient (β) for the association between perceived stress and emotional stress was reduced from 0.485 to 0.351 when sleep quality was added to the model.

The statistical significance of the mediating effect was further confirmed by the Sobel test. The SEM yielded a good fit to the observed data indicating the direct pathway from perceived stress to job burnout and the indirect pathway which was mediated by sleep quality. As is shown in **Figure 1**, the direct effect of perceived stress on job burnout was estimated in the model (the model fit of the data χ 2/df < 5, $p < 0.05$, GFI = 0.970, AGFI = 0.939, CFI = 0.976, TLI = 0.958, and RMSEA = 0.060), which was found to be statistically significant and positive ($\beta = 0.69$). As illustrated in **Figure 2** (the model fit of the data χ 2/df < 5, $p < 0.05$, GFI = 0.960, AGFI = 0.930, CFI = 0.968, TLI = 0.952, and RMSEA = 0.061), there existed statistically significant effects of sleep quality on both perceived stress ($\beta = 0.48$) and job burnout ($\beta = 0.29$). The path coefficients of perceived stress on job burnout were significantly reduced ($\beta = 0.56$) when sleep quality was modeled as a mediator. The bias-corrected and accelerated bootstrap test revealed that sleep quality had a significant mediating effect on the relationship between perceived stress and job burnout (a * b = 0.139, BCa 95%, CI: 0.110∼0.174). Thus, it was confirmed that perceived stress might not only directly affect job burnout but could also exert a significant indirect effect on job burnout via sleep quality.

DISCUSSION

Based on our knowledge, this study was the first to explore the relationship between perceived stress, sleep quality and job burnout among Chinese nurses and also the first to examine sleep quality as a mediator in the relationship between perceived stress and job burnout. Results of this study illustrated that 66.34% of Chinese nurses experienced burnout, which is similar to the finding of another cross-sectional study conducted among nurses working in municipal hospitals in China reporting that 68.1% of Chinese nurses suffered from burnout (15). One study involving 10,319 medical-surgical nurses of 303 hospitals in US, UK, Canada and Germany found an incidence of burnout ranging from 32% in Scotland to 54% in US (33). Also, it was reported that 20–40% of Australian nurses had burnout symptoms (34, 35), while findings from another cross-sectional study showed that Australian nurses experienced higher burnout than their Chinese counterparts (36). Burnout among nurses has become a prevalent problem which needs to be taken seriously and addressed in both developed and developing countries.

TABLE 3 | The hierarchical linear regression analysis of job burnout.

	Job burnout			EE			DE			PA		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Block 1 Demographic characteristics												
Age (<30 vs. ≥30)	−0.042	−0.049	−0.078*	−0.010	0.002	0.038	−0.019	−0.008	0.023	−0.068	−0.062	−0.064
Gender (male vs. female)	0.007	0.013	0.013	−0.044	−0.035	−0.036	−0.007	0.000	0.000	−0.073*	−0.068*	−0.068*
Marital status (Married or Cohabiting vs. others)	0.011	−0.019	−0.022	0.021	−0.022	−0.021	0.001	−0.036	−0.035	0.022	−0.001	−0.001
Education (Junior college and below vs. Bachelor degree and above)	−0.019	−0.034	−0.054	−0.032	−0.010	0.009	−0.026	−0.007	0.010	−0.102**	−0.091**	−0.091**
Monthly income												
(<3,000 *vs.* ≥3,000)	−0.034	−0.036	−0.039	−0.001	0.004	0.007	0.037	0.041	0.044	−0.052	−0.050	−0.050
Block 2 Perceived stress		0.328**	0.201**		0.485**	0.351**		0.416**	0.301**		0.256**	0.262**
Block 3 Sleep quality			0.391**			0.413**			0.356**			−0.019
R^2	0.004	0.110	0.244	0.005	0.236	0.385	0.002	0.173	0.284	0.035	0.099	0.099
Adjusted R^2	−0.001	0.105	0.239	0.000	0.231	0.381	−0.003	0.168	0.279	0.033	0.097	0.096
ΔR^2	0.004	0.106	0.134	0.005	0.231	0.150	0.002	0.171	0.111	0.035	0.064	0.000

**Significant at the 0.05 level (two-tailed); **Significant at the 0.01 level (two-tailed). EE, Emotional exhaustion; DE, Depersonalization; PA, Personal accomplishment; PS, Perceived stress; SQ, Sleep quality.*

FIGURE 1 | Structural equation modeling of perceived stress and job burnout.

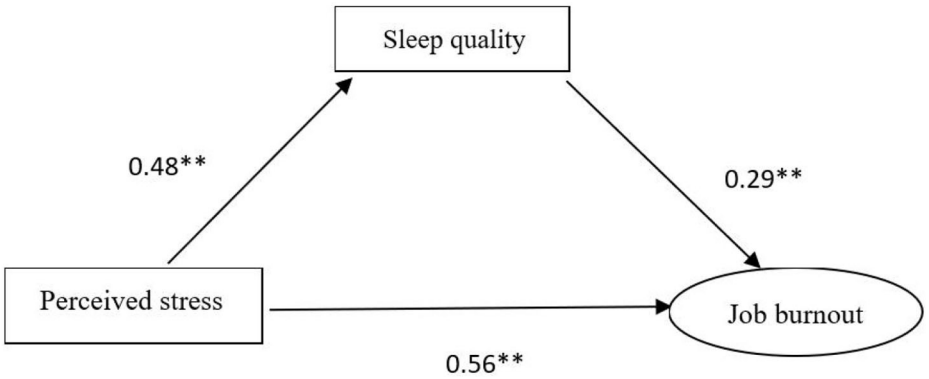

FIGURE 2 | Structural equation modeling of the mediating role of sleep quality on the relationship between perceived stress and job burnout.

Our study revealed that perceived stress has exhibited a strong positive relationship with burnout among Chinese nurses. The association between burnout and stress could be bidirectional, though burnout has typically been considered as a response to job-related stress (37, 38). It has been suggested that the occurrence of burnout might convert a previously enjoyable activity into a repelling source of stress (37). Victims of burnout are susceptible to low energy and chronic fatigue, which might lead to exhaustion during the day and poor sleep at night. From the emotional perspective, those with burnout tend to experience emotional depletion and difficulty feeling positive emotions. Feeling emotionally depleted may also give rise to tension and generalize negative attitudes to other aspects of life (37). From the physiological level, one's appraisals play an important role eliciting their physiological responses, which may also affect appraisal and reappraisal as part of feedback loop. That

is, bodily responses of fatigue contribute to the generation and reinforcement of appraisals of overload (37). This finding lends support to existing studies conducted among dental students (39), athletes (40), and teachers (41) in different countries indicating that cognitive appraisals of stressors could play a part in determining one's susceptibility to burnout. Previous studies have suggested that stress in and of itself is neutral (42) and it is the perception or appraisal of stress that plays a determining role in whether stressors have a positive or negative impact (25). One's response to stressors is determined by his perception of the stressfulness instead of the objective stressful events (26). Whether an event or a situation is appraised as threatening or challenging depends on one's availability of coping resources or if there exists an imbalance between demands and resources for a prolonged period of time (25).

Despite the fact that China's healthcare system is undergoing rapid development, there still exist a multitude of challenges that remain to be addressed. The percentage of the population aged 60 and over in China exceeded 12% in 2012 and an increasing trend of age-standardized mortality rates due to non-communicable diseases were observed (43), which put enormous strain on China's nursing system (44). Moreover, due to rapid socioeconomic growth and increased lifespan, there is an increasing demand for better-quality health care in China, with patients seeking more specific and personalized health-care services (45), which results in an increase in the workload of the nursing staff to deliver high-quality nursing care to meet the patients' needs (46). On the other hand, although the density of registered nurses per 1,000 population in China increased dramatically from 1.52 to 2.54 during the time from 2010 to 2016 (47), it still significantly outnumbered by US and countries in Europe (48). It has been reported that the nurse and midwife ratio per 1,000 population is approximately 12.66 in Australia and 8.33 in UK in 2016 and approximately 8.55 in US in 2015 (49). Prior research has documented that the likelihood of burnout was increased by 23% due to each additional patient a nurse must attend to (33). Meanwhile, the frequent occurrence of workplace violence against medical workers in recent years in Chinese hospitals, which has been attributed to various causes including lack of adequate primary health-care system and effective physician-patient communication (50), has also been linked to higher incidences of burnout among Chinese nurses (51). As mentioned above, nurses in China have been exposed to excessive workload and requirements combined with inadequate staffing and limited resources; this increases the likelihood of nurses' appraising their situation as stressful, which might in turn contribute to higher levels of burnout among Chinese nurses.

Our study also extends the existing literature by examining sleep quality as a mediator in the relationship between perceived stress and burnout among nurses. Prior studies showed that poor sleep quality (52, 53) or inadequate sleep (54) and perceived stress (55) were risk factors for burnout among medical student population. Perceived pressure and sleep were related to burnout among faculty at doctoral research universities (56). A recent cross-sectional study conducted among osteopathic medical students also found that higher perceived stress and poorer sleep quality were associated with all three dimensions of burnout (57). Results of our study reveals that perceived stress might not only exert a direct effect on burnout, but could also have indirect effect on burnout through sleep quality, indicating that nurses with higher levels of perceived stress tend to report poorer sleep quality and there is an increased risk on the development of burnout. This finding confirms previous studies revealing the positive correlation between perceived stress and poor sleep quality (58, 59). A possible explanation might be that sleep has been revealed to play a vital role in restoring daily functioning and regulating emotional experiences, which could mediate the relationship between stress and negative effects of burnout and help the brain process emotionally stressful events in adaptive ways (60). Sleep quality influences how individuals react to stressful events, for there is evidence showing the link between sleep deprivation and increased sensitivity to stressful stimuli and events (60) and lack of sufficient healthy sleep may result in the increase of negative emotional reactivity and reduce positive reactions to positive events (61). Inversely, one's response to daytime stressful events involves the ability to disengage from active wake processing, which could prevent the normal sleep process from being initiated (60). This could explain the bidirectionality of poor sleep quality and the perception of stress.

Meanwhile, the present study lends support to prior research conducted among nurses (62) and physicians (63, 64) confirming the finding that poor sleep quality was positively correlated with burnout. This might be due to the reason that burnout, based on the Conservation of Resources (COR) Theory (65), results from a continuous loss of resources that individuals lack the opportunities to replenish, whereas sleep can serve to halt the spiral of resource loss and contribute to the obtainment of other resources (such as good performance) (64). The dysregulation of hypothalamic–pituitary–adrenal (HPA) axis, which is commonly observed both among individuals reporting burnout and among those with sleep disturbances, might partially explain the relationship existing between sleep quality and burnout (64). It has been suggested that poor sleep quality is associated with a hyperactive state which is also integral in burnout and may cause an increased activation of the HPA axis, giving rise to a prolonged increase in the allostatic load (66). An increased activation of the HPA axis, which is the central stress response system and responsible for one's long-term adaptation to stress, could play a mediating role in the relationship between burnout and sleep disturbance (67). Another explanation might be that impaired sleep is closely related to sustained cognitive activation, or the inability to unwind or disengage from thoughts of work during leisure time, which was also found to predict burnout (68). An incomplete recovery pathway was shown to link from work demands to impaired sleep and, in the long run, to the development of burnout (68).

LIMITATIONS

This study is subject to several limitations despite the above-mentioned strengths. First, the cross-sectional design of this study provides no evidence for the existence of causal relationships between perceived stress, sleep quality and burnout.

The associations among stress, sleep and burnout might be bidirectional. Whereas, it is plausible that perceived stress exerted effects on burnout both directly and indirectly through the mediating role of sleep quality, it might be just as likely that burnout leads to perceived stress mediated by poor sleep quality. Further prospective studies are therefore necessary to clarify the directions of the associations among perceived stress, sleep quality and burnout. Second, the potential response bias of the self-reported measures used in this study may lead to an underestimation or overestimation of the associations between the variables. Third, all nurses participating in this study were recruited from public tertiary hospitals in Liaoning Province in Northeast China. The generalizability of the study results to a broader nursing population requires confirmation by further research.

CONCLUSIONS

This study represents the first attempt to explore sleep quality as a mediator in the relationship between perceived stress and job burnout among Chinese nurses. Our finding reveals that both perceived stress and poor sleep quality exhibited strong positive associations with burnout among Chinese nurses and perceived stress might exert effects on burnout both directly and indirectly through the mediating role of sleep quality. It could therefore be implied that efforts to reduce burnout among nurses might be expected to benefit from interventions for coping with perceived stress rather than the less readily modifiable work-related factors. Also, it is advisable that resources to promote healthy sleep practices should be provided at the organizational level (63) and more importance should be attached to sleep health for reducing burnout among the nursing staff.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee on Human Experimentation of China Medical University. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XY conceptualized, designed and supervised the project. YS reviewed the literature and wrote the manuscript. FY collected, analyzed, and interpreted the data. KS provided assistance and revised the manuscript. All authors read and approved the final manuscript.

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Resilience and Stress in Later Life: A Network Analysis Approach Depicting Complex Interactions of Resilience Resources and Stress-Related Risk Factors in Older Adults

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Background: Emerging systemic approaches on resilience propose that a person's or group's adaptability to significant stress relies on a network of interdependent resources. However, little knowledge exists on systemic resilience in older survivors of early-life adversity (ELA) and how ELA affects their resource network in later life.

Objective: This study investigated how ELA may be linked to the interplay of resources and stress-related risk factors in later life.

Research Design and Methods: Data from $N = 235$ older adults ($M_{age} = 70.43$ years; 46.40% female) were assessed. Half the participants were affected by ELA through compulsory social measures and placements in childhood, and/or adolescence ("risk group"). The other half were age-matched, non-affected participants ("control group"). Using psychometric instruments, a set of resilience-supporting resources in later life and current stress indices were assessed. Regularized partial correlation networks examined the interplay of resources in both groups, whilst also considering the impact of stress.

Results: Both groups demonstrated only positive resource interrelations. Although the control group showed more possible resource connections, the groups did not significantly differ in the overall strength of connections. While group-specific resource interrelations were identified, self-esteem was observed to be the most important resource for the network interconnectedness of both groups. The risk group network showed a higher vulnerability to current stress.

Discussion and Implications: Network analysis is a useful approach in the examination of the complex interrelationships between resilience resources and stress-related risk factors in older adulthood.

Keywords: resilience resources, network analysis, early-life adversity, stress-related risk factors, later life

INTRODUCTION

While resilience research experienced an exponential growth in the last three decades, a consensus has yet to be achieved regarding how to define, conceptualize, or quantify the psychological construct of resilience (Southwick et al., 2014; Snijders et al., 2018). Nevertheless, nowadays, most experts would agree that resilience is a common and ordinary phenomenon, describing positive adaptation to negative life circumstances, and the relative stability (or swift recovery) of psychosocial, mental, and physical functioning following exceptionally stressful periods or situations (e.g., Masten, 2001; Bonanno, 2004; Bonanno et al., 2011; Southwick et al., 2014; Liu et al., 2017). Significant research interest has been placed on the identification of protective and promotive processes, and factors that underpin an individual's resilience, such as individual characteristics, assets, and resources (Ungar, 2019).

Traditional Conceptualizations of Resilience

In the early beginnings of resilience research (e.g., Anthony, 1974; Garmezy et al., 1984; Werner and Smith, 1992), the focus was predominantly on the identification of particular personality traits (e.g., charisma) in children (Anthony, 1974). The aim was to understand why some "invulnerable" children were seemingly unaffected by adversity (Cowen and Work, 1988), by demonstrating "...positive child development despite the exposure to multiple risk factors and adversity" (Luthar et al., 2015, p. 247). Resilience research has since come a long way beyond the investigation of outstanding personality attributes in young individuals (Masten, 2014; Southwick et al., 2014). For instance, the inclusion of a social-ecological perspective (Ungar, 2011) has broadened the scope of resilience research to the prediction of positive outcomes after exceptional stress, facilitated by a diverse set of individual (e.g., coping skills) and external (e.g., social support) psychosocial resilience factors and processes (Iacoviello and Charney, 2014; Liu et al., 2017; Snijders et al., 2018). As the concept of resilience advanced, (high) resilience came to be understood as having a meaningful and effective collection of resilience factors for overcoming a specific stressful situation (Ungar, 2011). The fundamental idea behind this definition of resilience is the assumption of accumulation, i.e., that the more resilience factors the individual possesses, the more resilient the individual (Hobfoll, 1989, 2001).

Recent Conceptualizations of Resilience

More recent conceptualizations of resilience go beyond the assumption of accumulated resilience factors, instead emphasizing protective, and promotive processes, and factors that are mutually dependent on and influence each other (Rutter, 2012; Masten, 2014; Ungar, 2018). Within this perspective, resilience can be conceptualized as a complex network of differentially interrelated resource systems (i.e., internal systems such as biological, physiological, psychological; external systems such as social, cultural, environmental); each of which consists of resources that interact within and across systems. Depending on the stress context, the resources within an individual's resilience network interact and can enhance or hinder each other in their ability to make an individual more or less resilient (Ungar, 2017).

Resilience Networks

Research has only very recently begun to investigate resilience networks due to recent methodological advancements in network analysis (Costantini et al., 2015; Epskamp and Fried, 2018). Examples of such research include the examination of the interplay of resilience items and domains within a resilience questionnaire (Briganti and Linkowski, 2020), as well as the interplay of resilience, and risk factors (Fritz et al., 2018). Given the scarcity of research in this area, the latter study by Fritz et al. (2018) was used as a model upon which the current study could build. The authors applied a network analysis to examine the interrelations of various empirically supported psychosocial resilience factors (e.g., self-esteem, family cohesion) in adolescent survivors of childhood adversity and non-affected control participants. Results showed that depending on the history of childhood adversity, resilience factors were differentially interconnected with each other and their interconnectivity was further influenced by current distress. More specifically, the survivor group generally showed more negative interrelations between the resources, and their network was more negatively impacted by current distress. This suggests a deficiently functioning and vulnerable resilience network of the survivor group (Fritz et al., 2018). These findings indicate that resilience factors not only have the potential to impact each other, but can also affect, and be affected by (external) risk factors, resulting in differential outcomes.

Gaps in the Research on Resilience Networks

In fact, the vast majority of previous studies on resilience have generally been conducted with (high-risk) children, adolescents, and to some extent, young adults. Comparatively less knowledge exists on resilience in older adulthood and to the best of the authors' knowledge, no studies exist on the network analysis of resilience factors in older survivors of early-life adversity (ELA). In light of reports that resilience processes appear to differ between younger and older adults (e.g., Gooding et al., 2012), resilience factors identified in younger samples may not simply be assumed or adopted in research with older individuals. Given the global demographic changes towards an aging population, combined with the increasing awareness of the impact of ELA on health into old age, and the potential for resilience to shield against the negative impact of (age-related) chronic conditions (Manning et al., 2014); it is of great societal and scientific relevance to advance the understanding of resilience resources and networks in later life.

Building on the research by Fritz et al. (2018), an extensive literature search was conducted to identify psychological resilience factors in older adults and provide an empirical basis for the inclusion of resources into the network analysis of the current study. The following factors were repeatedly identified by previous studies as important in the resilience process or

outcome of older individuals with experiences of (childhood) maltreatment or adversity: *Socio-economic status (SES) and SES-related resources* (Tran et al., 2013; Pietrzak et al., 2014; Martin et al., 2015; Thoma et al., 2019), *conscientiousness* (Baek et al., 2016; Thoma et al., 2019), *positive affect/emotions* (MacLeod et al., 2016; Thoma et al., 2019), *optimism* (Martin et al., 2015; MacLeod et al., 2016; Höltge et al., 2018; Thoma et al., 2019), *social support (SS) and related factors* (Pietrzak et al., 2014; Maercker et al., 2016; Beutel et al., 2017; Höltge et al., 2018; Snijders et al., 2018), *self-esteem* (Gallacher et al., 2012; Thoma et al., 2019), *self-efficacy* (Tran et al., 2013; Martin et al., 2015; Maercker et al., 2016; Höltge et al., 2018), and *self-compassion* (Höltge et al., 2019a,b; Thoma et al., 2019).

Aims of the Current Study

It is the overarching goal of the present study to explore the structure and functioning of a resilience network, consisting of a selected set of resilience resources, in two samples of older adults with different ELA backgrounds. More specifically, this study aims to compare a network of resilience resources in a group of older adults with experiences of maltreatment and adversity within the context of child welfare practices, with that of a non-affected, age-matched control group. Furthermore, to compare the impact of stress-related risk factors on the network architecture of both groups, current stress load and stress symptoms will be included into the network models. It is commonly acknowledged that repeated and chronic stress, particularly when exposed to early in life can lead to a sensitization of the psychobiological (stress-)systems (Lupien et al., 2009). This in turn increases the vulnerability and sensitivity to future stress experiences and as such, heightens the probability for future (psycho-)pathology (McEwen, 1998; McLaughlin et al., 2010; Betz et al., 2020). It is therefore hypothesised that stress will have a differential impact on the two network models due to expected differences in the stress vulnerability of the risk and control groups. Investigating (a) the potentially different architecture of resilience, and (b) the impact of current stress on the resilience network in risk vs. non-risk individuals will help to identify key resilience resources. This could ultimately help facilitate a more efficient and resourceful targeting of protective measures in clinical interventions.

MATERIALS AND METHODS

This study was conducted at the University of Zurich, Switzerland, as part of the larger project "Differential aging trajectories in high-risk individuals with past experiences of early adversity." The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Arts and Social Sciences in the University of Zurich (ID: 19.4.3).

Recruitment

Individuals with a background in child welfare practices ("risk group") and non-affected individuals ("control group"), who were aged 50 years or older and were native Swiss German speakers, were recruited between July and December 2019. Individuals in the risk group were included if they were affected by compulsory social measures and/or placements (CSMP) in Switzerland before the age of 18 years, for a minimum duration of 1 year.

Risk Group

The CSMP of minors mostly entailed the placement of children and adolescents into foster care (e.g., children's homes, foster families) or institutions (e.g., closed psychiatric or penal institutions) (The Federal Office of Justice, 2020). The CSMP practices lasted up until 1981 and originally stemmed from a welfare concept, in which local authorities aimed to shelter minors from social norm "violations" (by their parents), such as extreme poverty, single motherhood, gipsy origin, or substance addiction of one of the parents (Leuenberger and Seglias, 2008). However, in many cases the CSMP practices were implemented arbitrarily, with many families being forcefully separated by the coercive and often traumatic removal of minors from their mothers and fathers (Leuenberger and Seglias, 2008). Previous studies conducted with Swiss individuals affected by CSMP in the last century found that growing up in foster care families and institutions was commonly associated with a broad range of stress experiences, including maltreatment and adversity (for example, see Kuhlman et al., 2013). Furthermore, children in foster care often had to work hard for their living. These children often had to work full days as farm workers, which also gave them the name *Verdingkinder* or "child slaves" (Leuenberger and Seglias, 2008). In addition, they were often deprived of proper nutrition, social contact with peers, and scholarly or vocational education. Former Verdingkinder lived isolated on the margins of society, were often bullied for coming from broken families or wearing dirty clothes, and were generally considered members of the lowest social class (Leuenberger and Seglias, 2008).

Most of the participants in the risk group were recruited by the *Swiss Federal Office of Justice* (SFOJ), the office at which individuals formerly affected by CSMP up until 1981 could apply for solidarity payments. The SFOJ compiled a list of individuals who had previously agreed to be contacted for research purposes, which was given to the project lead (MVT). An information letter about the study objectives was sent to potential participants with the invitation to contact the research team in the case of interest in study participation. Some participants in the risk group were recruited by contacting individuals who were publicly available due to their active public engagement as a survivor, as well as by word-of-mouth recommendations.

Control Group

The recruitment of the age-matched control participants included the posting of flyers, the contacting of individuals in the sample pool of the University Research Priority Program *Dynamics of Healthy Aging* of the University of Zurich, as well as via word-of-mouth recommendations.

Procedure

In the case of interest, potential participants contacted the study screening team. If all inclusion criteria were met, two face-to-face

appointments were scheduled (lasting no longer than 2 h each), and an information package was sent out. The latter included detailed information about the study, the informed consent, and questionnaires to assess basic socio-demographic and health information. The study site (University of Zurich, their homes, other location) was chosen by the participants on the basis of their personal preferences/mobility.

Upon arrival, final open questions were answered and the informed content was signed. The first assessment (A1) then started for the risk group with an interview collecting basic information regarding their particular experiences in the context of CSMP, followed by a structured clinical interview to assess a broad range of mental disorders. With the exception of the CSMP-related assessment, the procedure of the control group paralleled that of the risk group. All interviewers were specifically trained to conduct the interviews. At the end of A1, participant were given a questionnaire package to be filled-out and brought back to the second appointment (A2), which was scheduled within 7 days. The A2 consisted of the assessment of a broad set of information on ELA and maltreatment, lifetime stress and trauma, health, well-being, functional abilities, resilience, and cognition. As with A1, A2 lasted a maximum of 2 h. At the end of A2, participants were reimbursed with 240—Swiss Francs (approximately $250).

Instruments

A broad set of psychometric instruments were used in the larger project. Only those relevant for this study are presented in the following section, separated into instruments for risk factors, resilience resources, and outcome. Reliability statistics for all instruments and their correlations can be found in **Table 1**.

Risk Factors

Stress

To obtain an index for current stress, two self-report sub-scales of the German Stress and Coping Inventory were used (SCI, Satow, 2012). The sub-scale "total stress load" is a composite scale of the first three sub-scales ("stress due to uncertainty," "stress due to overload," and "stress due to loss and actual negative events"), which assess stress within the last 3 months (21 items). The sub-scale "physical and psychological stress symptoms" assessed symptoms within the last 6 months (13 items). Symptom 9 (desire for sex) was excluded in the current analysis as n = 31 participants did not answer this question (potentially due to the sensitive nature of this question for an older sample). Higher values in both sub-scales are indicative of higher stress load (potential score range: 21–147) and more physical and psychological stress symptoms (potential score range, excluding symptom 9: 12–48).

Resilience Resources

Socio-Economic Status

The *MacArthur Scale of Subjective Social Status* (Adler et al., 2000) provided an index for SES. It consists of a "ladder" (scale: 1–10) on which participants can place an "X" representing where they see themselves relative to others on the symbolic social ladder. Placing oneself on a higher step of the ladder is indicative of perceiving oneself as being closer to the highest social class (10), with respect to money, education, and occupation.

Conscientiousness

Conscientiousness is defined by high levels of self-control, persistence, goal-achievement, and problem-solving (McCrae and John, 1992), qualities which may be instrumental in coping with adversity and facilitating a more favorable, resilient outcome. The personality factor "conscientiousness" (Cons) was assessed with the German version of the *Big Five Inventory-10* (Rammstedt and John, 2007). Higher values in this sub-scale are indicative of a higher expression of "conscientiousness" (potential score range: 2–10).

Positive Affect

To assess "positive affect" (PA), the German version (Krohne et al., 1996) of the *Positive and Negative Affect Schedule* was used (Watson et al., 1988). Higher values are indicative of more PA (potential score range: 10–50).

Optimism

Optimism can be defined as an individual's tendency to have favorable expectations toward future events and outcomes (Carver et al., 2010). To obtain an index for "optimism" (OPT), the German version (Glaesmer et al., 2012) of the *Life Orientation Test-Revised* was administered (Scheier et al., 1994). Higher values of the sum score are indicative of higher levels of optimism (potential score range: 0–24).

Social Support

To assess "social support" (SS), the German short form of the *Social Support Questionnaire* was applied (Fydrich et al., 2009). Higher values are indicative of higher perceived emotional and material SS, and higher social integration (potential score range: 14–70).

Self-Esteem

Self-esteem is defined as having a positive attitude toward oneself, feeling that one has good qualities, and being a person of worth (Rosenberg, 1979). The "self-esteem" (SeEs) index was obtained using the revised German version of the *Rosenberg Self-Esteem Scale* (von Collani and Herzberg, 2003). Higher scores are indicative of higher levels of self-esteem (0–30).

Self-Efficacy

Self-efficacy (SeEf) is defined as an individual's belief that they are capable of coping with difficult circumstances (Schwarzer and Jerusalem, 2010). To obtain a measure for SeEf, the German version (Luszczynska et al., 2005) of the Generalized *Self-Efficacy Scale* was applied (Schwarzer and Jerusalem, 2010). Higher scores indicate higher values in SeEf (potential score range: 10–40).

Self-Compassion

Self-compassion (SCS) is defined as the way an individual treats themselves with warmth, compassion, and kindness in the event of failure or suffering (e.g., Raes et al., 2011). In order to assess "self-compassion" (SCS), the short form German version (Hupfeld and Ruffieux, 2011) of the *Self-Compassion Scale* was used (Raes et al., 2011). Higher values are indicative of greater levels of SCS (potential score range: 12–60).

TABLE 1 | Scale characteristics.

	Ω [CI]	SES	Cons	PA	OPT	SS	SeEs	SeEf	SCS	SL	SSY
Group	–	−0.33*	0.08	−0.15	−0.23*	−0.12	−0.13	−0.06	−0.11	0.24*	0.30*
SES	–	–	0.09	0.31*	0.42*	0.29*	0.40*	0.32*	0.34*	−0.53*	−0.50*
Cons	0.24[a]		–	0.17	0.09	0.14	0.21*	0.19*	0.12	−0.03	−0.07
PA	0.91 [0.89;0.92]			–	0.50*	0.36*	0.58*	0.52*	0.49*	−0.30*	−0.49*
OPT	0.75 [0.71;0.80]				–	0.40*	0.58*	0.49*	0.62*	−0.56*	−0.58*
SS	0.96 [0.95;0.96]					–	0.35*	0.32*	0.27*	−0.27*	−0.29*
SeEs	0.90 [0.88;0.92]						–	0.57*	0.75*	−0.48*	−0.56*
SeEf	0.93 [0.92;0.95]							–	0.54*	−0.32*	−0.42*
SCS	0.80 [0.76;0.83]								–	−0.46*	−0.56*
SL	0.95 [0.94;0.96]									–	0.68*
SSY	0.89 [0.87;0.91]										–

Group, control group was set as the reference group; SES, subjective socio-economic status; Cons, conscientiousness; PA, positive affect; OPT, optimism; SS, social support; SeEs, self-esteem; SeEf, self-efficacy; SCS, self-compassion; SL, stress load; SSY, stress symptoms. Ω [CI], Omega reliability coefficient with confidence interval for ordinal scaled items.

[a]*The scale for conscientiousness consists of two ordinal variables; therefore Spearman Brown coefficient was used. Correlations are adjusted for multiple testing.*

*$p < 0.05$.

Outcome

Satisfaction With Life

As an outcome measure, satisfaction with life (SWL) was assessed as an index of subjective well-being, using the German version (Glaesmer et al., 2011) of the *Satisfaction with Life Scale* (Diener et al., 1985). Higher scores indicate higher levels of subjective well-being (potential score range: 5–35).

Data Analysis

Statistical analyses were conducted using R (version 3.6.0). The pre-processing of the data involved missing value analyses and checking the distribution of the model indicators. Participants missing complete scales were excluded from the analysis. Expectation maximization imputation was used for participants who had up to two items missing. A non-paranormal transformation was conducted to normalize the skewed distributions for conscientiousness, SS, and self-esteem (Liu et al., 2009).

Network Analysis

Overall, six network models were estimated. A network was estimated that included all resources and the group variable that indicated the experience of ELA (**Figure 1**). For this model, the group variable was set as 0 for the control group (indicating the reference group) and 1 for the risk group. In this case, for example, a negative relationship between the group variable and another variable in the model would indicate that ELA leads to a lower score on the other variable. Furthermore, separate resource networks were estimated for the control group and the risk group (**Figures 2A,B**, respectively); a variability network was estimated, indicating how much the two groups differed in their resource associations (**Figure 3**); and separate networks were estimated for the control group and the risk group, including all resources, as well as current stress load, and stress symptoms (**Figures 4A,B**, respectively).

A network analysis estimates unique relationships between all model indicators. Regularized partial correlation networks were analyzed for all six models, as these are better suited for network estimation with lower sample sizes than unregularized networks (Epskamp et al., 2017; Williams et al., 2019). A partial correlation network consists of two elements: (1) nodes, which represent the model indicators, and (2) edges, which indicate the conditional dependence between two model indicators. The networks were estimated using *bootnet* (Epskamp et al., 2018), by applying the least absolute shrinkage and selection operator with the Extended Bayesian Information Criterion (EBICglasso). This obtained parsimonious networks with meaningful edges and minimized the estimation of false positive node associations (Epskamp and Fried, 2018). EBICglasso also shrinks small and spurious edges to zero using a penalty that was set to a recommended value of 0.5 in all analyses (Epskamp and Fried, 2018).

In addition to graphically investigating specific node associations and overall patterns in the networks, several measures were investigated to compare the two groups. First, the order of node strength centrality was compared for model 2A and 2B using Pearson correlations. Strength centrality indicates the absolute interconnectivity of one node with all its connected nodes (Epskamp and Fried, 2018). Nodes with a high strength centrality have relatively many and strong associations with other nodes, and are therefore important for the structure and functioning of a network. Second, a variability network was estimated, which shows how much the edge weights differ between the two groups (for model 2A and 2B), based on each edge weight's standard deviation across both groups (Fried et al., 2018). Third, the global strength of each entire network was compared by summing all absolute edge weights per network (overall network connectivity). This was applied to models 2A and 2B, as well as 4A and 4B, by controlling for stress load and stress symptoms (Fried et al., 2018). This facilitates three meaningful comparisons: Comparing 2A and 2B indicates which of the two groups has a weaker/stronger connected network; whilst the difference in the total strength centrality between 2A and 4A, and 2B and 4B, respectively, indicates how much each group's network becomes negatively impacted

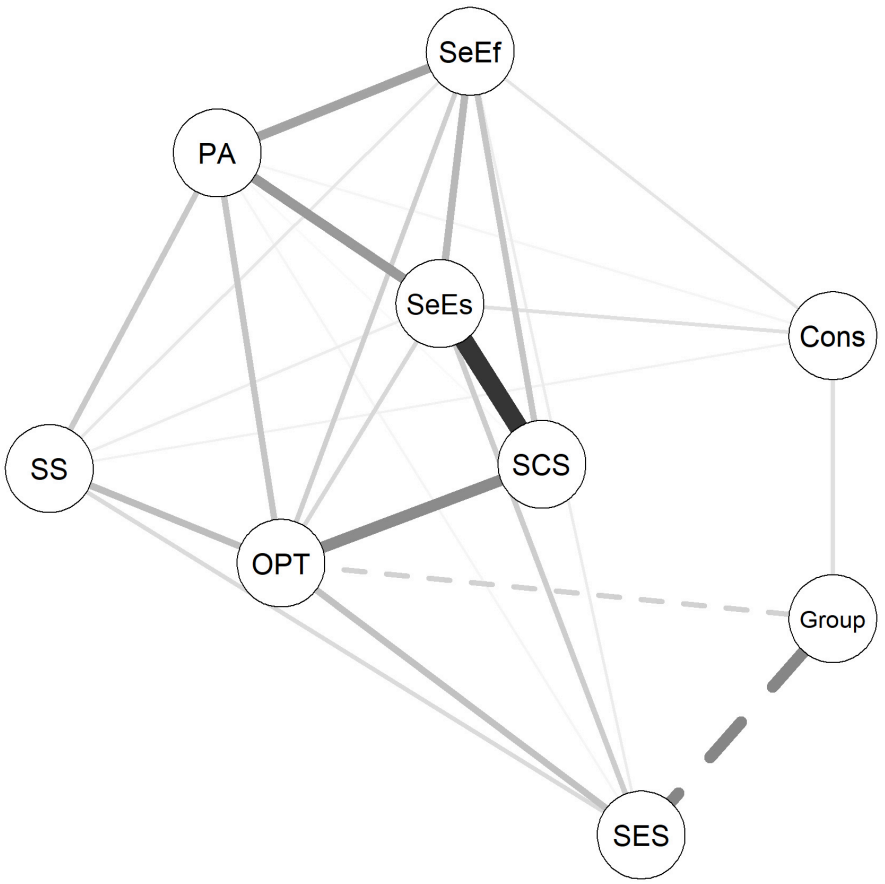

FIGURE 1 | The effect of ELA on resilience resources. Group: control group was set as the reference group. Solid lines indicate positive relationships, dashed lines indicate negative relationships. The wider the line, the stronger the relationship. SES, subjective socio-economic status; Cons, conscientiousness; PA, positive affect; OPT, optimism; SS, social support; SeEs, self-esteem; SeEf, self-efficacy; SCS, self-compassion.

by current stress load and symptoms. Fourth, differences in network structure and global strength between model 2A and 2B, and model 4A and 4B, were formally tested with a permutation test, using the R package *NetworkComparisonTest* (van Borkulo et al., 2017). The tests were performed with 5,000 permutations.

The R package *bootnet* (Epskamp et al., 2017) was further used to visualize the networks and to provide insight into the stability of the strength centrality estimates and accuracy of the edge weight estimates. Case-dropping subset bootstrap was used to test for strength centrality stability. To indicate sufficient stability, a correlation of at least 0.25, but better 0.50 or higher, must be estimated between the original network and the subsets (Epskamp et al., 2017). The accuracy of edge weights is indicated via bootstrapped confidence intervals (bCI). The smaller the bCI, the more accurate is the estimate. However, an edge can still be interpreted in the case of wide bCIs when analyzing a regularized network, as using EBICglasso selects the most meaningful edges. The layout of the given models is a result of the Fruchterman–Reingold algorithm, which places nodes with stronger connections closer together. For a better comparability of the models, the average layout of model 4A and 4B was used for all models.

RESULTS

Sample Demographics

The samples consisted of $n = 125$ (51.2% female) for the control group and $n = 110$ (40.9% female) for the risk group. Twenty-two participants in the risk group were excluded due to missing values for complete scales. As can be seen in **Table 2**, the two groups significantly differed ($p < 0.005$) in their optimism, stress load, stress symptoms, and SWL. The risk group showed lower values in all resilience resources and the outcome variable SWL, and higher values in the stress indicators. The risk group also reported (non-significant) lower SS, PA, self-esteem, and SCS. Age, consciousness, and SeEf showed similar values in both groups.

The Effect of ELA on Resilience Resources

Figure 1 shows which resources within the analyzed resource network are affected by the experience of ELA in the risk group.

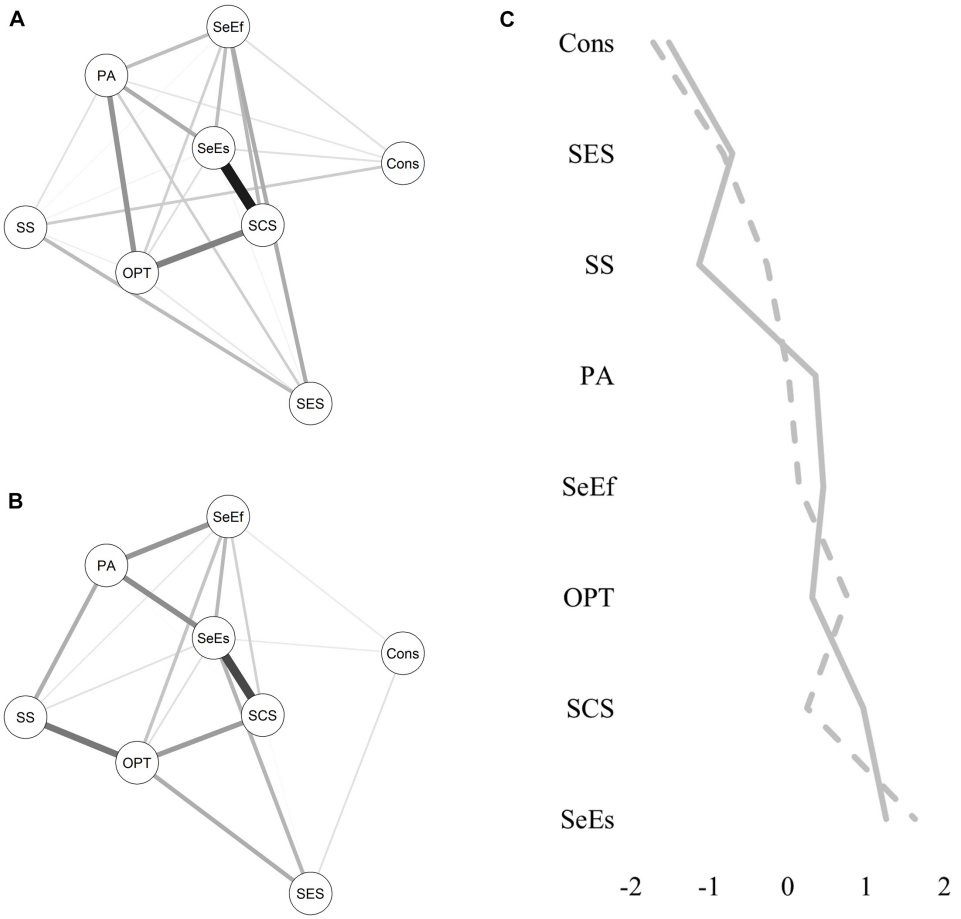

FIGURE 2 | Group-specific resource networks. **(A)** Control group network. **(B)** Risk group network. Solid lines indicate positive relationships. The wider the line, the stronger the relationship. SES, subjective socio-economic status; Cons, conscientiousness; PA, positive affect; OPT, optimism; SS, social support; SeEs, self-esteem; SeEf, self-efficacy; SCS, self-compassion. **(C)** Standardized resource strength centrality: solid line indicates control group, dashed line indicates risk group. The higher and more positive the value, the higher the strength centrality of a resource.

It suggests that being in the risk group is associated with a lower subjective SES and optimism (negative edges), and a higher conscientiousness (positive edge).

Resource Network of the Control and Risk Groups

Figures 2A (control group) and 2B (risk group) show the group-specific resource networks. The connected resources show only positive associations in both groups. The strongest resource connection was estimated for SCS and self-esteem in the control group (0.55) and the risk group (0.44) (see **Table 3** for the edge weights of the resource networks for both groups). Overall, the network of the control group shows more connections (51% of possible connections) than the risk group (40% of possible connections), but both show the same average edge weight of 0.09. This implies that while the two groups differ in the number of resource connections, on average, the resources are equally strongly associated when taking into account all possible resource associations in the entire network. When considering only the existing connections, the average edge weight of the control group is lower (0.13) compared to the risk group (0.16).

Figure 2C shows the strength centrality profiles for both groups. The largest differences in strength centrality were found for SS and SCS: SS has a higher strength centrality in the risk group, while SCS has a higher strength centrality in the control group. In both groups, conscientiousness was the least strength-central resource and self-esteem was the strongest strength-central resource. The strength profiles of both groups showed a correlation of $r = 0.87$, indicating that the two groups show a similar ranking of the resources in terms of their strength centrality.

Figure 3 shows the variability network, which indicates how much the control group and risk group differed in their resource associations. The permutation test identified significant differences ($p < 0.05$) for the association between SS and optimism, as well as between subjective SES and SeEf. The association between PA and optimism also showed a strong, but non-significant difference between the models. As shown in **Table 3**, the connection between SS and optimism was

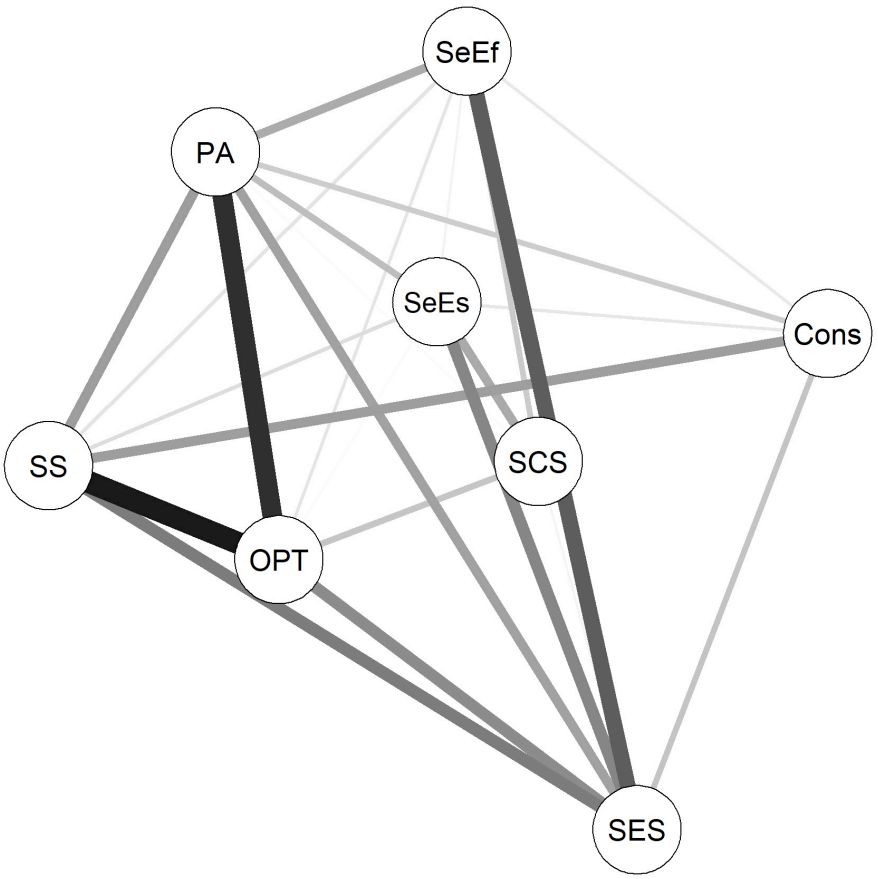

FIGURE 3 | Variability network. The wider the line, the stronger the difference in edge weight between the two groups. SES, subjective socio-economic status; Cons, conscientiousness; PA, positive affect; OPT, optimism; SS, social support; SeEs, self-esteem; SeEf, self-efficacy; SCS, self-compassion.

stronger for the risk group than the control group. However, the connections between subjective SES and SeEf, and between PA and optimism, exist only for the control group, but not for the risk group.

Overall, the permutation test shows that the two resource networks did not significantly differ in their structure ($M = 0.29$, $p = 0.17$), or global strength ($S = 0.13$, $p = 0.73$). The global strength was 3.00 for the control group and 2.87 for the risk group.

The Influence of Current Stress on the Resource Network of the Control and Risk Groups

The control group shows nine negative associations between the stress indicators and the resources (**Figure 4A**) while the risk group shows eleven negative associations (**Figure 4B**). Furthermore, the stress indicators show overall stronger negative associations with the resources in the control group network (−1.07), compared to the risk group (−0.97). The permutation test shows that the two resource networks (including the stress indicators) did not significantly differ in their structure ($M = 0.26$, $p = 0.35$), or global strength ($S = 0.67$, $p = 0.09$). The global strength was 4.02 for the control group and 3.36 for the risk group.

Figure 4C gives a detailed overview of how strongly the resources are affected by stress load and stress symptoms combined. The subjective SES of both groups are strongly negatively affected by stress, although the influence of stress on SES is higher in the risk group. For the control group, the strongest negative influence of stress was on optimism (−0.38), PA (−0.26), and subjective SES (−0.26). For the risk group, the strongest negative influence of stress was on subjective SES (−0.34), SCS (−0.20), and self-esteem (−0.20).

In a further step, the associations between the resources of each group were explored when controlling for the influence of current stress. In comparison to the resource-only network (models 2A and 2B), the global strength of the risk group's resource network (in which current stress was controlled for) showed a stronger decline (a decrease of −0.81 to a global strength of 2.06) than the control group (a decrease of −0.46 to a global strength of 2.54). This indicates that current stress has a greater weakening effect on the resource network of the risk group compared to that of the control group. It is also of note that in the risk group, conscientiousness loses all its connections to other resources when controlling for current

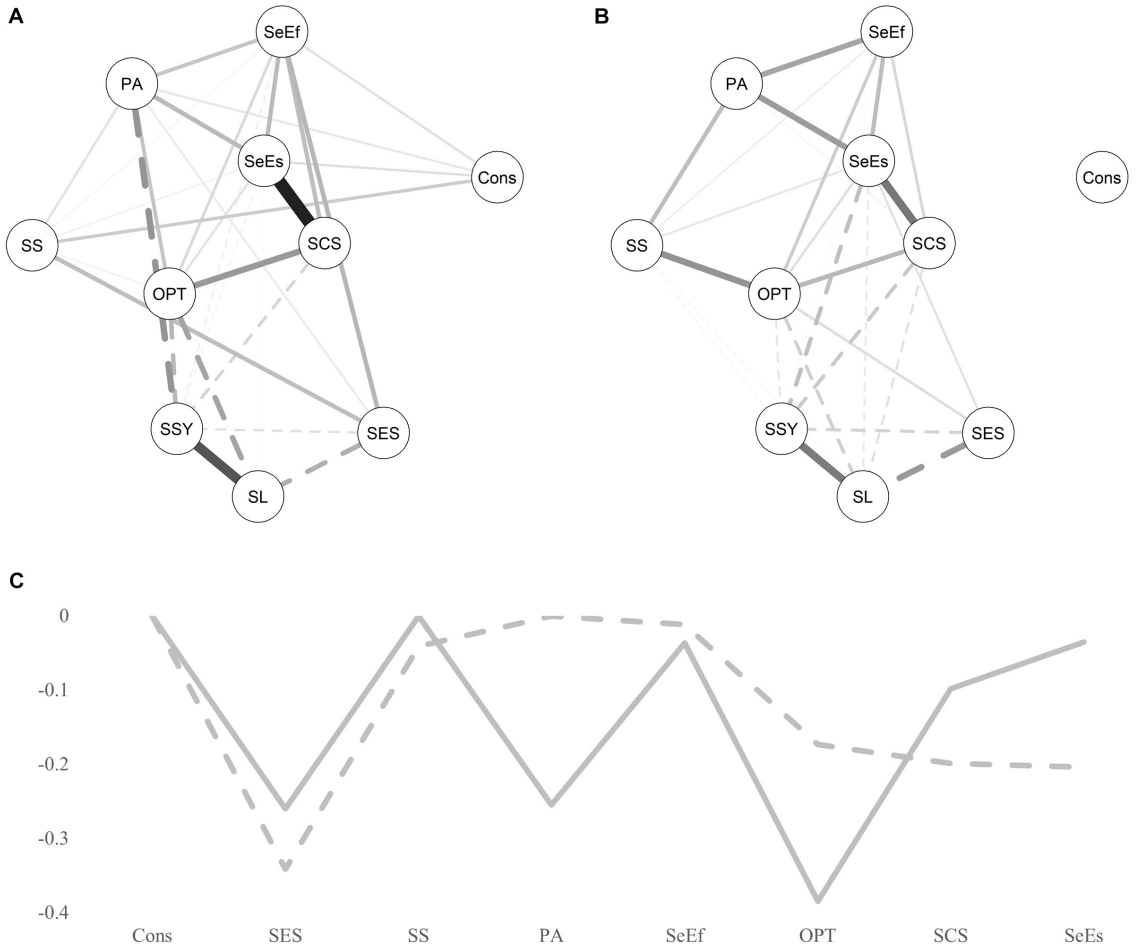

FIGURE 4 | Effect of current stress on the group's resource networks. **(A)** Control group network. **(B)** Risk group network. Solid lines indicate positive relationships, dashed lines indicate negative relationships. The wider the edge, the stronger the relationship. SES, subjective socio-economic status; Cons, conscientiousness; PA, positive affect; OPT, optimism; SS, social support; SeEs, self-esteem; SeEf, self-efficacy; SCS, self-compassion; SL, stress load; SSY, stress symptoms. **(C)** Joint negative effect of stress load and stress symptoms on resources. Solid line indicates control group, dashed line indicates risk group. The higher the negative value, the stronger the negative effect of current stress on a resource.

stress (comparing model 2B with model 4B), indicating that current stress likely affects the associations of conscientiousness with other resources.

Stability and Accuracy Analyses

The graphical outputs for the stability and accuracy analyses can be found in the online Supplementary Material. The strength centrality stability analyses showed that all correlations between the original networks and their respective subsets were above the minimum requirement of 0.25, with most above 0.50. The average range of the bootstrapped CIs around the edge weight estimates ranged from 0.21 to 0.25.

DISCUSSION

The overall goal of this study was to compare a network of a selected set of resilience factors in two samples of older adults with varying backgrounds in early childhood adversity. Furthermore, this study aimed to investigate the impact of stress-related risk factors on the networks of the two groups. The results showed that the networks of both groups demonstrated only positive resilience resource interrelations. While the control group appeared to have a more connected network, no significant differences were observed in the network structure and global strength when compared to the risk group. In addition, although both groups showed a high level of similarity with respect to the importance of the resilience resources for the connectedness of their networks, group-specific resilience resource relationships were also identified. Furthermore, while the inclusion of current stress indices resulted in more overall negative connections in the risk group, the negative relationships observed in the control group were somewhat stronger. Finally, the results revealed that the interconnectedness of the risk groups' resource network became weaker due to the inclusion of current stress.

ELA and Resource Interconnectivity

As this was a cross-sectional study, the direction of influence of two model indicators is causally undirected in the network. As such, the results are interpreted by the assumption of which factor is the predictor and which is the outcome (Fried et al., 2018). Regarding the descriptive statistics, the risk group mostly showed lower levels of resilience resources, higher stress levels (stress load and stress symptoms), as well as lower well-being. This was as expected and in line with previous studies on other ELA survivors (Nurius et al., 2015; Carr et al., 2018).

The connection between group and subjective SES, and optimism was negative, and the connection between group and conscientiousness was positive. This implies that having been brought up in the context of child welfare practices (and as such, having had a higher risk for the experience of adversity and maltreatment), may be associated with lower subjective SES and optimism in later life. This is in line with previous research conducted with comparable samples of individuals affected by child welfare practices in other countries in the last century (e.g., Sigal et al., 2003; Kuhlman et al., 2013; Lueger-Schuster et al., 2018; Carr et al., 2019). The finding that the risk group was linked to lower levels of optimism in the current study is also supported by previous research, which found a negative relationship between childhood emotional maltreatment and dispositional optimism in older adulthood (Broekhof et al., 2015). The positive connection observed between a background in childhood welfare practices and conscientiousness was unexpected and may provide tentative evidence for stress-related resilience in this sample. Results also showed that although the network of the risk group had fewer connections, the overall strength of connections and network structure did not significantly differ in comparison to the control group. Given that the risk group reported significantly higher stress levels (stress load, physical, and mental stress symptoms) and lower levels of well-being, these findings may suggest that having more, though somewhat weaker connections is characteristic of a better functioning resource network than having few strong connections.

The network analyses further revealed that the resource networks of both the risk and control groups showed only positive interrelations. This finding contrasts with a previous network analysis study on resilience and childhood adversity in adolescents, which identified negative interrelations between several resilience factors (Fritz et al., 2018). One explanation may be related to the differing ages of the investigated samples. It may be that in an older sample, individuals have had more experience across the life course with successfully utilizing and strengthening their resource network, which may in turn help to buffer against the impact of ELA. However, to make more concrete conclusions, future research should investigate the impact of adversity on resilience resource networks at varying stages across the life span.

Both groups also showed a similar strength centrality profile, indicating that roughly the same resources were important for the functioning of both networks. Self-esteem was the most important resilience factor for both groups' network interconnectedness. As such, self-esteem may be an optimal resilience resource upon which to focus to facilitate an efficient targeting of protective measures and clinical interventions for older adults dealing with the negative effects of ELA. Conscientiousness, on the other hand, showed the least relationships with other resilience resources. Thus, while its positive connections may suggest a protective influence, its reduced interrelatedness with other resilience resources imply that conscientiousness may be less important for consideration as a primary target of resilience interventions.

In relation to edge weights, the strongest differences were found between SS and optimism, PA, and optimism, as well as SeEf, and subjective SES. The connection between SS and optimism was stronger for the risk group than the control group. Adversity experiences in an individual's early environment can shape their expectations regarding affect regulation, social interactions, support availability, and help-seeking behaviors (Riggs, 2010; Lee et al., 2015). Thus, it may be that due to higher levels of interpersonally experienced adversity in their childhood

TABLE 2 | Sample characteristics.

	Control group *M* (SD)	Risk group *M* (SD)
Age	70.60 (9.68)	70.25 (12.09)
SES[a]	6	5
Cons	8.37 (1.45)	8.59 (1.38)
PA	34.10 (7.19)	31.87 (7.82)
OPT*	16.92 (4.47)	14.77 (4.45)
SS	56.32 (10.94)	53.17 (12.79)
SeEs	22.95 (4.99)	21.53 (5.38)
SeEf	29.89 (4.70)	29.29 (5.99)
SCS	41.28 (7.70)	39.64 (6.95)
SL*	33.26 (15.88)	41.83 (19.14)
SSY*	18.14 (5.41)	21.83 (6.53)
SWL*	24.95 (7.00)	21.15 (7.62)

SES, subjective socio-economic status; Cons, conscientiousness; PA, positive affect; OPT, optimism; SS, social support; SeEs, self-esteem; SeEf, self-efficacy; SCS, self-compassion; SL, stress load; SSY, stress symptoms; SWL, satisfaction with life.

[a]*Median displayed due to ordinal scale.*

**$p < 0.005$ using Mann-Whitney U Test with Benjamini Hochberg False Discovery Rate correction.*

TABLE 3 | Edge weights for the resource networks for both groups (model 2a and 2b).

	SES	Cons	PA	OPT	SS	SeEs	SeEf	SCS
SES	–	0.07	0	0.19	0	0.17	0	0.01
Cons	0	–	0	0	0	0.05	0.05	0
PA	0.12	0.06	–	0	0.19	0.27	0.25	0
OPT	0.05	0	0.26	–	0.32	0.07	0.14	0.23
SS	0.16	0.12	0.07	0.04	–	0.07	0.05	0
SeEs	0.03	0.08	0.19	0.08	0.03	–	0.17	0.44
SeEf	0.20	0.07	0.15	0.11	0.02	0.16	–	0.11
SCS	0	0	0	0.30	0	0.55	0.17	–

SES, subjective socio-economic status; Cons, conscientiousness; PA, positive affect; OPT, optimism; SS, social support; SeEs, self-esteem; SeEf, self-efficacy; SCS, self-compassion. Below diagonal, edge weights for control group. Above diagonal, edge weights for risk group.

and adolescence, individuals in the risk group place a higher value on SS in their adult life. In support of this, previous research with a similar sample of Swiss Verdingkinder found that SS predicted resilience in later life (Maercker et al., 2016). This finding is further supported by the observed connection with optimism in the current study, which has been shown in the literature to be associated with the capacity to seek and utilize SS (Carver and Scheier, 2014). Therefore, in facilitating more resilient outcomes, survivors of ELA in welfare-contexts may uniquely benefit by drawing upon the resilience resources of optimism and SS.

The control group additionally demonstrated positive connections between PA and optimism, as well as SeEf and subjective SES; connections that were not observed in the risk group. It may be that given their background in ELA, individuals in the risk group are less able than the control group to engage with internal resilience resources that are reliant on the self, such as PA or SeEf. In support of this, recent research with a similar sample of $N = 220$ of adult survivors of institutional ELA in Austria found that institutional childhood abuse predicted lower levels of SeEf and self-esteem in adulthood. The study concluded that prolonged exposure to ELA in such institutional welfare settings may lead to reduced self-beliefs and beliefs in one's ability to succeed in difficult situations (Weindl et al., 2018). However, given the novelty of the present findings, additional longitudinal, group-comparison research is needed to explore this further.

Current Stress and Resource Interconnectivity

A critical facet of resilience research is the examination of the interplay between risk factors and resilience (Windle, 2011). In the current study, the risk factors of current stress load and stress symptoms were introduced into the resilience resources network. The resource network of the risk group appeared to be more vulnerable to current stressors, as indicated by a stronger decline in overall resource interconnectivity. This in line with the findings of Fritz and colleagues, which identified a more dysfunctional resilience network in the adolescent survivors of childhood adversity when controlling for the influence of current stress (Fritz et al., 2018). However, in the current study, although more negative relationships were observed between the stress-related risk factors and resilience resources in the risk group, the strength of the negative connections was stronger in the control group. Within the risk group, the resilience resources most severely affected by current stress were those related to the self, such as SCS, subjective SES, and self-esteem. This contrasts with the network of the control group, in which current stress more severely affected the resilience resources linked to positivity, i.e., PA and optimism. While the influence of stress on positivity may be an expected finding (e.g., Schilling and Diehl, 2014; Horiuchi et al., 2018), the impact on the self in survivors of child welfare adversity is of particular interest. It may be that individuals who experienced child adversity and degradation in these welfare contexts have a vulnerable self-perception and are more susceptible to the impact of current stress. This may highlight potential targets for intervention, such as improved self-perception, SCS, and self-esteem. However, given the lack of causality in the data, additional research should further investigate this novel finding.

Strenghts

This is the first study to apply network analysis in the investigation of resilience resources and their interplay with stress, in a sample of older survivors of ELA experienced within the context of child welfare practises. Previous research using network analysis to examine resilience networks has thus far only assessed children and adolescents (e.g., Fritz et al., 2018). By examining adults and older adults, this study expands the literature on resilience resource networks into older life stages. In addition, the application of a dynamic resilience conceptualization allowed for the modeling of a complex network of differentially interrelated internal and external resource systems. While future (longitudinal) research is need to replicate these findings, the identification of a positive network of resilience resources may be beneficial in highlighting potential targets for clinical intervention with adult survivors of ELA. An additional strength was the use of an age-matched control group not affected by welfare-related adversity in childhood. This allowed for a comparison of the resilience resource networks and interpretations to be made specific to adult survivors of ELA in the context of welfare practices. Furthermore, using network analysis in the realm of resilience research adds another crucial perspective to the characteristics of resources and resilience interventions: rather than identifying only the most effective resources in a stressful context, network analysis provides the opportunity to identify the central resources. Central resources are important for the sustainability of a network and are a potential target to efficiently influence other resources.

LIMITATIONS

Several limitations warrant consideration when interpreting the results of this study. This study used a cross-sectional design, which hinders the determination of a causal relationship between the model indicators. Resilience is best assessed using a longitudinal approach to capture its dynamic nature (Snijders et al., 2018), as resilience can develop and change over time in response to different stressful contexts (Luthar et al., 2000). Furthermore, the sample size was relatively small, which limited the power and scope of the analysis. For instance, small homogeneous groups can lead to a low differential variability, which can make it less likely to detect resource connections within a network (e.g., Fried and Nesse, 2014). Also, due to the context-specificity of resilience (Ungar, 2011), even the networks between institutionalized children and children who lived with foster families might differ, which could not be tested in the current study due to the limited sample size. Related to this, the ELA of this historic risk sample, i.e., being raised in the context of welfare practices, is a rather specific form of

adversity and may hinder the generalizability of the findings. As such, this study should be replicated across larger samples and within differing ELA contexts in order to empirically test the generalizability of the network structure. Furthermore, although this study assessed psychological and social resources in older age, additional contextual resources for resilience could be added in a next step. For instance, an ecological systems' approach to resilience would warrant the addition of socio-ecological resources, such as community, cultural, or economic resources (Ungar, 2018).

CONCLUSION

To the best of the authors' knowledge, this was the first study to apply network analysis to explore the interplay of resilience and risk factors in two age-matched, older samples with differing backgrounds in ELA. Although the network model approach is still a comparably young perspective in the field of psychopathology, and resilience research in particular (see Fried and Cramer, 2017 for challenges of the network perspective); this study has shown that it is a suitable methodology for the examination of the interrelationships between resilience and risk factors. The findings of the current study identified a complex network of resilience resources, highlighting resources that were more strongly connected in the separate resilience networks of both the risk and control groups. It further examined the interplay between resilience resources and risk factors (i.e., current stress) and demonstrated group-specific changes in the resilience networks following the introduction of the risk factors. Despite the difficulties with causal interpretation of findings, network analysis is a useful tool for moving forward resilience research by providing essential steps toward a better understanding of the complex construct of resilience.

DATA AVAILABILITY STATEMENT

Due to the sensitive nature of the data, the data cannot be published on a public data repository. The raw data will instead be held in the university archives in accordance with the ethical regulations. Requests to access the datasets should be directed to m.thoma@psychologie.uzh.ch; jan.holtge@dal.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Faculty of Arts and Social Sciences in the University of Zurich (ID: 19.4.3). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT, JH, and SR conceived the idea for the study and were responsible for the conception and design of the study. MT and SR were managing data collection. CE and VP were involved in data collection. JH conducted all data analysis. MT and JH wrote the manuscript together-both contributed equally to the manuscript. SR profoundly contributed to the writing of the manuscript and the interpretation of the data. SR proofread the manuscript. All authors critically revised the manuscript before submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2020.580969/full#supplementary-material

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REVIEW
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Neural Mechanisms Underlying the Rewarding and Therapeutic Effects of Ketamine as a Treatment for Alcohol Use Disorder

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Alcohol use disorder (AUD) is the most prevalent substance use disorder and causes a significant global burden. Relapse rates remain incredibly high after decades of attempting to develop novel treatment options that have failed to produce increased rates of sobriety. Ketamine has emerged as a potential treatment for AUD following its success as a therapeutic agent for depression, demonstrated by several preclinical studies showing that acute administration reduced alcohol intake in rodents. As such, ketamine's therapeutic effects for AUD are now being investigated in clinical trials with the hope of it being efficacious in prolonging sobriety from alcohol in humans (ClinicalTrials.gov, Identifier: NCT01558063). Importantly, ketamine's antidepressant effects only last for about 1-week and because AUD is a lifelong disorder, repeated treatment regimens would be necessary to maintain sobriety. This raises questions regarding its safety for AUD treatment since ketamine itself has the potential for addiction. Therefore, this review aims to summarize the neuroadaptations related to alcohol's addictive properties as well as ketamine's therapeutic and addictive properties. To do this, the focus will be on reward-related brain regions such as the nucleus accumbens (NAc), dorsal striatum, prefrontal cortex (PFC), hippocampus, and ventral tegmental area (VTA) to understand how acute vs. chronic exposure will alter reward signaling over time. Additionally, evidence from these studies will be summarized in both male and female subjects. Accordingly, this review aims to address the safety of repeated ketamine infusions for the treatment of AUD. Although more work about the safety of ketamine to treat AUD is warranted, we hope this review sheds light on some answers about the safety of repeated ketamine infusions.

Keywords: ketamine, alcohol use disorder (AUD), depression, addiction, mechanisms

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INTRODUCTION

Alcohol use disorder (AUD) is defined as a chronic relapsing brain disease arising from repeated cycles of compulsive alcohol use, withdrawal, and relapse (American Psychiatric Association, 2013; National Institute on Alcohol Abuse and Alcoholism, 2018). Even though a majority of the world's population has consumed alcohol at one point during their lifetime, only around 15% of people develop pathological drinking

patterns symptomatic of AUD, suggesting individual differences in susceptibility to AUD [Substance Abuse and Mental Health Services Administration (SAMHSA), (2015)]. Within this subset of individuals, relapse rates increase after long periods of alcohol abstinence since 60–75% of individuals relapse after 1-year, up to 80% after 3-years, and 90% after 4-years of attempted sobriety (Polich et al., 1981; Miller et al., 2001; Moos and Moos, 2006; Evren et al., 2010). These high relapse rates result from both low treatment-seeking, given that only around 8% of the 15 million adults suffering from AUD in the United States received any form of treatment in 2018, and the fact that currently available pharmacological treatment options are ineffective in the maintenance of long term sobriety (National Institute on Alcohol Abuse and Alcoholism, 2018; Carvalho et al., 2019).

Along with many neuropsychiatric disorders, AUD treatment yields the best results when specific psychosocial and pharmacological interventions are combined (Kranzler and Sakoya, 2018; Carvalho et al., 2019). Psychosocial interventions are more effective than pharmacological interventions given that only two of the top 10 effective treatment options were pharmacological including acamprosate, a $GABA_A$ receptor agonist, and naltrexone, a μ-opioid receptor antagonist (Miller and Wilbourne, 2002). Even within these effective pharmacological treatment options, efficacy is modest. A meta-analysis examining seven studies found no treatment effect when investigating the effect of acamprosate on heavy alcohol drinking (Jonas et al., 2014). The same meta-analysis only showed naltrexone to effectively reduce heavy drinking when orally administered at 50 mg but not when given orally at 100 mg or injected (Jonas et al., 2014). Even within studies testing 50 mg oral naltrexone, results were highly variable since around half of the studies analyzed showed no significant effect of treatment (Jonas et al., 2014). Finding effective treatments for AUD is compounded by methodological challenges that can significantly alter the assessment of treatment efficacy (Klemperer et al., 2018). For example, while the meta-analysis conducted in Jonas et al. (2014) showed only a modest treatment effect in one naltrexone-administered group across randomized clinical trials, another meta-analysis examining naltrexone's treatment efficacy within human laboratory studies showed a more significant treatment outcome for both craving and alcohol-drinking quantity, suggesting study characteristics can influence the assessment of treatment efficacy (Hendershot et al., 2017). More recently, other treatments such as sodium oxybate have shown significant treatment efficacy compared to placebo controls, particularly in patients with very high drinking risk level (van den Brink et al., 2018). However, one drawback to sodium oxybate for the treatment of AUD is its abuse potential since there have been reports of patients recreationally abusing it during treatment (van den Brink et al., 2018). As such, improving pharmacotherapies for AUD is necessary to reduce drinking and improve treatment outcomes.

Ketamine is a dissociative drug that acts primarily through NMDAR antagonism (Harrison and Simmonds, 1985). In the clinic, high dose ketamine [1–2 mg/kg, intravenous (i.v.)] is commonly used as an anesthetic since it has nociceptive properties and because its lack of impact on respiratory function eliminates the risk of overdose (Ivani et al., 2003). Recently, low dose ketamine (usually 0.5 mg/kg, i.v. over 40 min infusion) has shown great therapeutic benefit for patients suffering from treatment-resistant depression (TRD). Indeed, a single i.v. infusion of 0.5 mg/kg ketamine alleviates depressive-like symptoms within 2-h and has long-lasting effects for up to 2-weeks (Berman et al., 2000; Zarate et al., 2006). Furthermore, repeated low-dose ketamine infusions administered intermittently produced increased treatment response rates and sustained low-depressive scores, indicating that a repeated treatment regimen is more effective for treating TRD compared to a single ketamine infusion (Murrough et al., 2013; Shiroma et al., 2014). Following the success of low-dose ketamine for TRD, other investigators embarked on examining the potential clinical benefits of ketamine for the treatment of AUD (Yoon et al., 2019; ClinicalTrials.gov, Identifier: NCT03658330). The initiation of a clinical trial investigating ketamine as an AUD treatment option was supported by preclinical studies that previously showed acute, low-dose administration reduced alcohol intake in chronically drinking male and female rats (Sabino et al., 2013; Holleran et al., 2016; Rezvani et al., 2017, **Table 1**).

TABLE 1 | Summary of preclinical studies investigating the effect of ketamine administration on alcohol addictive-like behaviors.

Subject	Sex	Alcohol paradigm	Ketamine paradigm	Effect	Reference
Alcohol-preferring rats	M	Operant self-administration (10% v/v)	Acute: 10 mg/kg (i.p.) Acute: 20 mg/kg (i.p.)	No change Intake	Sabino et al. (2013)
C57BL6 mice	F	CA2BC10% + 2-week withdrawal	Acute: 3 mg/kg (i.p.)	Anxiety-like behavior (NSFT)	Holleran et al. (2016)
Alcohol-preferri ng rats	M,F	CA2BC10%	Acute: 5 mg/kg (i.p.) Acute: 7.5 mg/kg (i.p.) Acute: 10 mg/kg (i.p.)	%pref (M,F) Intake/ %pref (M,F) Intake/ %pref (M,F)	Rezvani et al. (2017)
Sprague–Dawley rats	M,F	IA2BC20% (High-drinkers) IA2BC20% (Low-drinkers)	Chronic: operant self-administration 0.5 mg/kg/inf (i.v.)	Intake/ %pref (M only) Intake/ %pref (F only)	Strong et al. (2019)

Acute, low-dose ketamine administration reduces alcohol intake and preference along with alleviating anxiety-like behavior induced by alcohol withdrawal in rodents of both sexes. Chronic operant self-administration of ketamine reduced alcohol intake and preference in male, but not female, high-drinkers while increasing alcohol intake and preference in female, but not male, low-drinkers. Abbreviations: CA2BC10%, continuous access 2-bottle choice (10% alcohol v/v); IA2BC20%, intermittent access 2-bottle choice (20% alcohol v/v); i.p., intraperitoneal; i.v., intravenous; NSFT, novelty suppressed feeding test.

One drawback of ketamine as a potential TRD treatment is the fact that, even at low doses, it causes feelings of dissociation, depersonalization, and, at times, mild hallucinations (see review by Strong and Kabbaj, 2018). However, in both people with a family history of AUD as well as alcohol-dependent patients, the dissociative symptoms are blunted following a single i.v. infusion of ketamine at the same dose used for TRD patients (Krystal et al., 2003; Petrakis et al., 2004). These effects are likely the result of long-lasting alterations in NMDAR function in these subsets of people since similar findings have been reported with other NMDAR antagonists. For example, people with a family history of AUD were found to be less sensitive to the dissociative effects of memantine, an NMDAR antagonist, and this effect was attributed to enhanced baseline NMDAR function within these individuals (Jamadar et al., 2012). The fact that people with AUD experience fewer dissociative symptoms from ketamine compared to TRD patients suggests that ketamine as an AUD treatment option may be more efficacious given fewer side effects.

Importantly, though, the studies referenced above investigated only the effects of a single infusion of ketamine. As with depression, AUD is a lifelong disorder and would require repeated ketamine infusions to maintain long term sobriety. This is significant given that repeated exposure to ketamine may have abuse potential as demonstrated by pre-clinical reports showing that rats will self-administer ketamine at doses as low as 0.1 mg/kg/infusion (De Luca and Badiani, 2011; Wright et al., 2017; Caffino et al., 2018). Furthermore, ketamine, a "club drug" known to be taken recreationally in combination with alcohol, has abuse potential in humans and is listed as a Schedule III drug. This raises questions about the safety of treating AUD with a known addictive agent since studies have shown that polysubstance abuse is common among users of club drugs, particularly with alcohol (Wu et al., 2006, 2009). Therefore, understanding the safety of such repeated treatment regimens in both male and female subjects is necessary before using repeated ketamine administration as a viable AUD treatment option. Given the success of ketamine for the treatment of depression, possible its efficacy for AUD would be highest in individuals suffering from comorbid addiction and depression. As such, the purpose of this review is to discuss neural mechanisms of alcohol and ketamine effects under acute and chronic regimens. Here, we will highlight cell-type, brain region, and circuit-specific changes that alcohol and/or ketamine induce that are relevant in mediating their addictive and therapeutic properties. By better understanding the neurobiology of chronic alcohol and ketamine exposure, we hope through this review to gain a better understanding of the safety of repeated ketamine infusions for the treatment of AUD.

NEURAL MECHANISMS OF ALCOHOL'S ADDICTIVE PROPERTIES

In general, drug addiction occurs through aberrant changes in synaptic and structural plasticity following repeated drug exposure. As such, neural mechanisms involved in acute drug exposure usually differ from those involved in chronic exposure. For alcohol, acute exposure leads, among other things, to NMDAR antagonism while chronic exposure potentiates these receptors (Lovinger et al., 1989; Floyd et al., 2003). While it seems paradoxical that a drug initially acting as an NMDAR antagonist could, over time, act as an NMDAR agonist, there are several potential mechanisms through which this might occur. The sections below will highlight alcohol-mediated changes in transmitter systems, receptors, and cell-type-specific potentiation.

The striatum is the main component of reward-related circuitry and is divided into the dorsal striatum with dorsomedial and dorsolateral subregions (DMS and DLS, respectively) and the ventral striatum that consists of the nucleus accumbens (NAc) and olfactory tubercle. Within the striatum, the principal neurons are GABAergic medium spiny neurons (MSNs) that are highly cell-type specific since 90–95% express either the dopamine 1 or 2 receptor (D1Rs or D2Rs; Gerfen et al., 1990; Le Moine et al., 1990; Lobo et al., 2006). Both MSN subtypes function through G-protein coupled processes in an opposing manner depending on their response to extracellular dopamine. D1Rs couple to stimulatory G-proteins (GαS) to facilitate the production of cyclic AMP (cAMP) and promote gene transcription. However, D2Rs couple to inhibitory G-proteins (Gαi) to inhibit cAMP production and gene transcription (Neve et al., 2004; Del'guidice et al., 2011). Within the striatum, the NAc is considered the hub of reward circuitry since it receives converging dopaminergic input from the ventral tegmental area (VTA) and glutamatergic input from regions such as the prefrontal cortex (PFC), hippocampus (HPC), and amygdala. Here, this review will focus on how acute vs. chronic alcohol exposure impacts NAc MSNs and briefly summarize the impact on DMS MSNs by summarizing how transmitter systems, receptors, and circuitry are affected.

Acute Alcohol Exposure

Acute alcohol exposure induces a net inhibitory effect within several brain regions through bimodal actions on both NMDA receptor blockade and a reduction in glutamate release (Lovinger et al., 1989; Carboni et al., 1993; Floyd et al., 2003). Blockade of NMDARs has been demonstrated in several preclinical studies through the measurement of NMDAR-mediated excitatory postsynaptic potentials/currents (EPSPs/EPSCs) in brain regions including the hippocampus, cortex, amygdala NAc, and dorsal striatum (DS; Calton et al., 1999; Maldve et al., 2002; Yaka et al., 2003; Kolb et al., 2005; Yin et al., 2007). Furthermore, the reduction in glutamate release within the striatum following acute alcohol exposure has been demonstrated through microdialysis studies in rats (Carboni et al., 1993). Together, the interaction between reduced glutamate along with NMDAR blockade indicates a reduction in excitatory neurotransmission following acute alcohol exposure.

Extracellular dopamine is increased within the NAc following acute alcohol exposure, as demonstrated by several preclinical studies using microdialysis to measure extracellular dopamine in rodents (Yoshimoto et al., 1992; Yan, 1999; Yim and Gonzales, 2000; Vena et al., 2016). Furthermore, acute alcohol-induced dopamine release occurred exclusively in the NAc since increased

extracellular dopamine levels were not observed in the dorsal striatum until alcohol was administered repeatedly (Vena et al., 2016). The increase in extracellular dopamine in the NAc was shown to be a result of increased dopamine release from the VTA rather than inhibition of dopamine reuptake within the NAc (Yim and Gonzales, 2000). The dopaminergic neurons of the VTA are under tonic control of GABAergic neurons within the same brain region, and it has shown that acute alcohol exposure depresses VTA GABAergic inhibitory postsynaptic currents (IPSCs; Xiao and Ye, 2008). Furthermore, a modulatory role of alcohol on mu-opioid receptors expressed on VTA GABAergic neurons has been shown, likely through increases in endogenous beta-endorphin levels (Méndez et al., 2001; Xiao and Ye, 2008; Jarjour et al., 2009). As a result, increased VTA dopamine release following acute alcohol exposure likely occurs, in part, as a result of enhanced opioidergic signaling on GABAergic neurons in the VTA to disinhibit nearby dopaminergic neurons. Together, these findings indicate that increased extracellular striatal dopamine activity as a result of increased VTA dopamine release mediates the rewarding effects of acute alcohol exposure.

Adenosine is a signaling molecule that is produced both intra- and extracellularly through the metabolism of adenosine triphosphate (ATP) *via* nucleotidase (Nam et al., 2013a). When produced intracellularly, it is released into the synapse through adenosine transporters, and the most prominent adenosine transporter known to play a role in alcohol's rewarding properties is equilibrative nucleoside transporter 1 (ENT1; Nam et al., 2013a). Extracellular adenosine can then bind to adenosine receptors expressed in a cell-type-specific manner on GABAergic MSNs, with adenosine 1 receptors (A1Rs) specific to D1-MSNs and adenosine 2a receptors (A2aRs) specific to D2-MSNs in the striatum (Dixon et al., 1996; Shen et al., 2008). Studies have shown that acute alcohol exposure increases levels of extracellular adenosine by blocking its reuptake through ENT1 (Nagy et al., 1990; Krauss et al., 1993). The increased extracellular adenosine then activates A2aRs on D2-MSNs, which function as stimulatory G-protein coupled receptors (G_s GPCRs), in contrast to D2Rs on D2R-containing MSNs, which are G_i GPCRs (Shen et al., 2008). As such, G_s-coupled D1Rs on D1R-containing MSNs and A2aRs on D2R-containing MSNs similarly stimulate intracellular signaling cascades that release intracellular stores of Ca^{2+} and activate cAMP-dependent gene transcription in the NAc (Swapna et al., 2016). Inhibitory D2 GPCRs form heteromers with A2aRs on D2R-containing MSNs and can modulate the stimulatory role of A2aRs based on the balance between extracellular adenosine and dopamine (Azdad et al., 2009; Swapna et al., 2016). Activation of the A2aR on this MSN subtype leads to the activation of adenylyl cyclase (AC) and increases the level of cyclic AMP (cAMP). Elevated cAMP activates the regulatory subunit of protein kinase A (PKA) and releases the catalytic subunit (C_α), which translocates from the Golgi to the nucleus, and remains there until alcohol exposure ends, where it increases gene expression, specifically by phosphorylating the Ser^{133} site of CREB to initiate transcription (Nestler, 2004). Interestingly, functional studies using either ENT1-null mice or pharmacologically inhibiting ENT1 in the dorsomedial striatum have shown increased alcohol consumption as a result of increased extracellular adenosine (Choi et al., 2004; Nam et al., 2013b). Together, these results suggest that adenosine signaling on D2R-containing MSNs may be important for the acquisition of alcohol-drinking behaviors.

In the NAc, one report showed that mice exposed to a single session of binge-like alcohol drinking displayed enhanced activation of D1R-containing MSNs through recruitment of the mammalian target of rapamycin (mTOR) signaling pathway (Beckley et al., 2016). Here, it was shown that D1R stimulation was enough to activate mTOR signaling (Beckley et al., 2016). Furthermore, mTOR pathway activation on this MSN subtype in the NAc led to increased translation of the GluA1 subunit of the AMPA receptor, which is critical for the induction of long-term potentiation (LTP; Kristensen et al., 2011). The same report showed that acute alcohol intake increased the trafficking of GluA2-lacking, Ca^{2+}-permeable AMPARs, thereby reducing the threshold for further potentiation of NAc D1-MSNs (Beckley et al., 2016). While acute alcohol administration is associated with reduced glutamatergic signaling, increased glutamate release in the NAc after repeated exposure to alcohol, which will be discussed below, would make D1-MSNs more susceptible to LTP induction. For example, one report identified Prosapip-1, a downstream signaling molecule of mTOR, as a target required for alcohol-dependent increases in NAc dendritic spine density and insertion of GluA2-lacking AMPARs and further showed that knockdown of Prosapip-1 in the NAc reduced alcohol self-administration in mice (Laguesse et al., 2017). Together, these studies show that acute alcohol exposure activates mTOR on NAc D1-MSNs through D1R stimulation, which activates downstream signaling cascades that make this MSN subtype more susceptible to future potentiation which is involved in alcohol intake and seeking behaviors. Overall, acute alcohol exposure appears to act on D1R-MSNs through increases in extracellular dopamine and on D2R-MSNs from increases in adenosine. Therefore, both MSN subtypes are likely involved in the initial phase of acute alcohol intake.

Chronic Alcohol Exposure

In the shift from acute to chronic alcohol exposure, each neurotransmitter system discussed above undergoes major changes. While acute alcohol exposure was associated with ENT1 blockade to produce increased extracellular adenosine, chronic alcohol exposure leads to a desensitization of the G_s-coupled A2aR (Gordon et al., 1986; Charness et al., 1988; Choi et al., 2004; Allen-Gipson et al., 2009), likely as the result of sustained increased levels of extracellular adenosine acting on A2aRs. In support of this, ENT1 knockout mice displayed a reduced function of the A2a receptor in the DMS, and intra-DMS infusions of an A2aR antagonist increased alcohol intake (Nam et al., 2013b). Along with receptor desensitization, other reports indicated that the adenosine transporter, ENT1, resumed normal function following chronic alcohol exposure *via* downregulation of ENT1 expression (Gordon et al., 1990; Sapru et al., 1994). As such, chronic alcohol exposure is associated with less activation of G_s-coupled A2aRs on D2R-containing MSNs, allowing the G_i-coupled D2R to have more of an impact on downstream signaling cascades and leading to inhibition of cAMP-PKA

mediated intracellular Ca^{2+} release and gene transcription in this MSN subtype (Swapna et al., 2016). Additionally, a recent study showed that systemic administration of an adenosine analog that activates A2aRs and inhibits ENT1 reduced alcohol intake in chronically drinking mice, suggesting that while A2aR activation may play a role in the acquisition of alcohol consumption, it may be less involved in regulating the maintenance of alcohol intake (Hong et al., 2019).

In people with a family history of AUD, the expectation of an alcohol reward is associated with increased dopamine release into the NAc (Kegeles et al., 2018). However, dopamine release in the NAc is decreased in AUD patients undergoing withdrawal (Volkow et al., 2007). This is in line with data from rats which showed that alcohol cue-seeking was associated with increased dopamine release in the NAc core and dorsolateral striatum but that chronic alcohol drinking itself did not increase dopamine release (Shnitko and Robinson, 2015). One study examining dopamine's role in associative learning in monkeys found that when exposed to a cue before a rewarding stimulus on the first trial, dopamine neurons increased firing following stimulus presentation as compared to the cue. Over time, however, these neurons began firing during the presentation of the cue, which always preceded the stimulus, and not for the reward itself (Fiorillo et al., 2003). This study is in line with what has been shown with alcohol; acute exposure increases dopamine release in the NAc while dopamine following chronic alcohol consumption increases more for alcohol-related cues. Nonetheless, dopamine release during alcohol-seeking behaviors would have stimulatory effects on D1R-containing MSNs and inhibitory effects on D2R-containing MSNs, inducing a net excitatory effect within the striatum. In one report examining cocaine, dopamine-mediated activation of D1R-containing NAc MSNs increased ΔfosB, a transcription factor considered a marker for addiction, through a feedforward loop involving calcium calmodulin II alpha (CaMKIIα) autophosphorylation of the FosB gene (Robison et al., 2013). Similarly, ΔfosB expression in the NAc is increased in D1R- but not D2R-containing MSNs following chronic alcohol intake and this may be mediated by dopamine's actions on D1R-containing MSNs (Lobo et al., 2013).

While acute alcohol reduces glutamate release and NMDAR-mediated EPSCs, chronic alcohol exposure is known to induce NMDAR-mediated plasticity exclusively on D1R-containing MSNs (Ji et al., 2017; Renteria et al., 2017, 2018). Electrophysiological studies have shown that chronic alcohol exposure leads to increased glutamatergic transmission within the NAc from the PFC, HPC, and amygdala (**Figure 1A**; Ji et al., 2017). Within the NAc, multiple reports have shown that chronic alcohol exposure led to increased firing of D1R-containing MSNs while not affecting D2R-containing MSNs in both the core and shell (**Figure 1B**; Renteria et al., 2017, 2018). These findings further showed increased NMDAR function on D1R- but not D2R-containing NAc MSNs, suggesting that increased NMDAR potentiation may drive the observed increases in neuronal firing (Renteria et al., 2017). Additionally, a recent report chemogenetically manipulated NAc D1R- vs. D2R-MSNs and showed that activation of D1R-containing NAc MSNs increased alcohol intake while inhibition of this MSN subtype decreased alcohol intake (Strong et al., unpublished). Importantly, these findings were extended to female rats for the first time (Strong et al., 2020). Additionally, activating D2R-containing NAc MSNs did not affect alcohol intake but inhibiting these MSNs increased intake in both sexes, suggesting a potential indirect compensatory activation of NAc D1R-containing MSNs as a result of inhibiting D2R-containing MSNs (Strong et al., 2020).

While it appears that D1R-containing MSNs within the NAc control alcohol intake, it remains unclear what intracellular signaling mechanisms contribute to these changes. As mentioned above, acute alcohol exposure led to mTOR pathway activation on D1R-containing neurons (Beckley et al., 2016). Following chronic alcohol intake, intra-NAc infusions of rapamycin, an mTOR antagonist, reduced alcohol intake in chronically drinking male mice (Cozzoli et al., 2016). While this study did not examine whether these effects were specific to D1R-containing MSNs within the NAc, it is clear that mTOR plays a regulatory role in alcohol intake in males. Interestingly, the same study showed that this is not the case in female mice since their alcohol intake was unaffected across a wide range of rapamycin doses, suggesting that mTOR may be a key regulator of alcohol's addictive properties in male but not female mice (Cozzoli et al., 2016). However, intra-NAc infusions of MTEP, a mGluR5 antagonist, did reduce alcohol intake in both male and female mice (Cozzoli et al., 2014). Together, these studies along with those mentioned above indicate sex similarities at the cellular and receptor level induced by alcohol, but differences in recruitment of intracellular signaling pathways. Interestingly, a study examining genetic alterations in alcoholic humans observed a sex-specific polymorphism of PI3K, a kinase that activates the mTOR signaling pathway, in males but not females, supporting the finding in the study mentioned above (Desrivieres et al., 2008). Future studies should examine downstream signaling pathways from mGluR5 involved in modulating alcohol intake in male and female subjects to better understand these sex differences. Furthermore, information about whether mTOR and mGluR5 activation are specific to D1R- or D2R-containing NAc MSNs is necessary to better understand mechanisms underlying alcohol's addictive properties.

Within the dorsomedial striatum (DMS), chronic alcohol intake led to increased glutamatergic transmission on D1R-containing MSNs and enhanced GABAergic transmission on D2R-containing MSNs (Figure 5B; Cheng et al., 2017). The same study showed that chemogenetic inhibition of D1R- and activation of D2R-containing MSNs reduced alcohol intake whereas activation of D1R- and inhibition of D2R-containing MSNs increased alcohol intake in male mice, suggesting that DMS MSNs bidirectionally control alcohol intake in a cell-type-specific manner (Figure 5B; Cheng et al., 2017). Within D1R-containing DMS MSNs, several reports have shown increased NMDAR potentiation through increased trafficking of the GluN2B regulatory subunit, which has increased conductance and channel open probability as mentioned above (Traynelis et al., 2010; Morisot and Ron, 2017). Previous reports indicate that increased GluN2B insertion enhances the activity of the NMDAR through phosphorylation of Fyn kinase

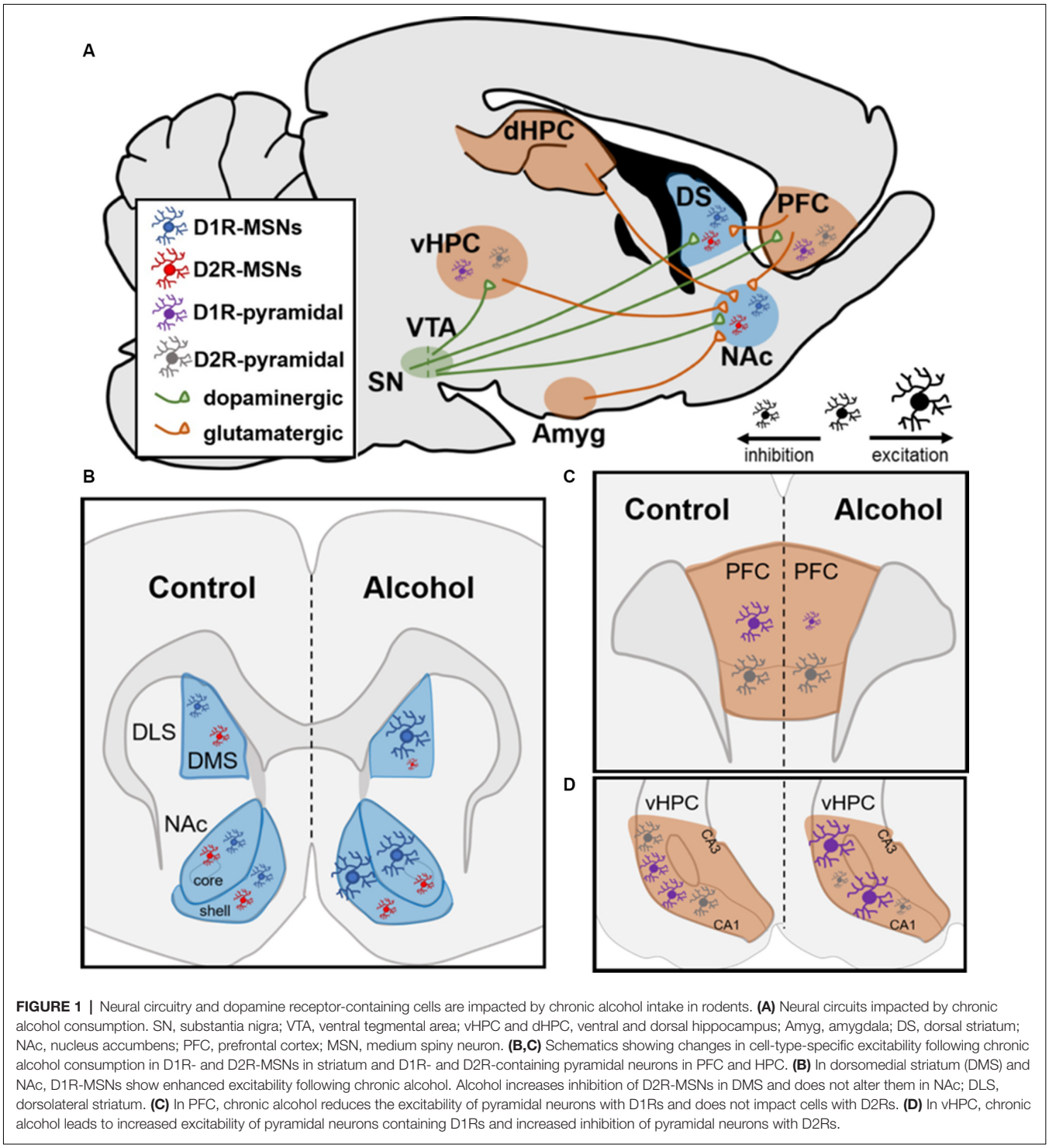

FIGURE 1 | Neural circuitry and dopamine receptor-containing cells are impacted by chronic alcohol intake in rodents. **(A)** Neural circuits impacted by chronic alcohol consumption. SN, substantia nigra; VTA, ventral tegmental area; vHPC and dHPC, ventral and dorsal hippocampus; Amyg, amygdala; DS, dorsal striatum; NAc, nucleus accumbens; PFC, prefrontal cortex; MSN, medium spiny neuron. **(B,C)** Schematics showing changes in cell-type-specific excitability following chronic alcohol consumption in D1R- and D2R-MSNs in striatum and D1R- and D2R-containing pyramidal neurons in PFC and HPC. **(B)** In dorsomedial striatum (DMS) and NAc, D1R-MSNs show enhanced excitability following chronic alcohol. Alcohol increases inhibition of D2R-MSNs in DMS and does not alter them in NAc; DLS, dorsolateral striatum. **(C)** In PFC, chronic alcohol reduces the excitability of pyramidal neurons with D1Rs and does not impact cells with D2Rs. **(D)** In vHPC, chronic alcohol leads to increased excitability of pyramidal neurons containing D1Rs and increased inhibition of pyramidal neurons with D2Rs.

(Trepanier et al., 2012). It has been shown that chronic exposure to alcohol leads to Fyn autophosphorylation in DMS through a PKA-mediated mechanism; PKA was shown to phosphorylate striatal enriched protein tyrosine phosphatase (STEP), which is a Fyn phosphatase (Wang et al., 2007; Gibb et al., 2011; Darcq et al., 2014). As a result of never getting dephosphorylated by STEP, Fyn continuously phosphorylates the GluN2B subunit of the NMDAR, which increases the channel's open probability and, thus, increasingly potentiates the cell over time (Morisot and Ron, 2017). Recently, these findings were extended to D1R-containing neurons in the DMS since it was shown that alcohol's enhanced glutamatergic transmission on these MSNs resulted from increased potentiation of NMDARs through the GluN2B subunit (Cheng et al., 2017). This same report suggested

that the enhanced GABAergic transmission on D2R-containing DMS MSNs resulted from increased activity of the $GABA_A$ receptor on these MSNs (Cheng et al., 2017). Together, these studies provide evidence for how DMS MSNs control alcohol intake in a cell-type-specific manner.

As mentioned above, PFC-NAc and HPC-NAc circuitry is impacted by chronic alcohol since these circuits display enhanced glutamatergic transmission compared to controls (Ji et al., 2017). One report using optogenetics showed that medial PFC (mPFC) to NAc core circuitry is involved in aversion-resistant alcohol intake but not alcohol intake in the absence of aversion (Seif et al., 2013). However, a recent study functionally ablating PFC glutamatergic projections to NAc using Diptheria toxin receptors showed that mPFC-NAc is necessary for cue-induced reinstatement of alcohol-seeking since blocking this circuitry abolished responding for alcohol-related cues (Keistler et al., 2017). Furthermore, Fos-positive nuclei in the mPFC increased during periods of alcohol abstinence, but not during periods of drinking, though the number of Fos-positive nuclei was shown to predict future alcohol-drinking amounts (George et al., 2012). Altogether, this data suggests that PFC-NAc circuitry may be less involved in alcohol intake itself and more involved in aversion-resistance to alcohol as well as reinstatement to alcohol-related cues. To date, no studies functionally manipulating HPC-NAc circuitry in the context of alcohol drinking exist. However, a recent study examining ventral hippocampus (vHPC) projections onto NAc shell D1R-containing MSNs showed that alcohol intake amount negatively correlated with LTD-induction, suggesting that increased alcohol intake is correlated with enhanced potentiation of NAc D1R-containing MSNs receiving inputs from vHPC (Kircher et al., 2019). The same study showed increased glutamate release from vHPC onto D1R-containing neurons in the NAc shell and the insertion of GluA2-lacking, Ca^{2+}-permeable AMPARs, though these effects were not correlated with the intake (Kircher et al., 2019). Studies functionally manipulating HPC-NAc circuitry are necessary to better understand the role this circuit plays in alcohol-drinking behaviors.

Along with NAc and dorsal striatum, subregions of the PFC and HPC contain excitatory pyramidal neurons that have a cell-type-specific expression of D1Rs and D2Rs (Wei et al., 2018). A recent report showed that within the vHPC, 90% of pyramidal neurons contained either D1Rs or D2Rs (Wei et al., 2018). Additionally, in the orbitofrontal cortex (OFC) of the PFC along with the dorsomedial PFC, 85% of pyramidal neurons contain D1Rs or D2Rs in a cell-type-specific manner (Wei et al., 2018). Like the NAc, both the vHPC and the PFC receive dopaminergic input from the VTA (Lisman and Grace, 2005). In contrast to what studies have reported within the striatum, D1R-containing neurons within the PFC experience reduced firing following chronic alcohol intake whereas D2R-containing neurons are unchanged by alcohol (**Figure 1C**; Trantham-Davidson et al., 2017). Along with these findings, a recent report found reduced glutamatergic excitatory neurotransmission from the OFC onto D1R-containing MSNs within the DMS while there was no change in glutamatergic excitatory input from these neurons to D2R-containing MSNs (**Figure 1A**; Renteria et al., 2018). This may suggest that the PFC-striatal circuitry is not a major contributing factor in the heightened excitability in D1R-containing neurons within the NAc and DMS following chronic alcohol intake. However, in chronically drinking male mice, pyramidal neurons in the vHPC containing D1Rs displayed increased firing whereas those with D2Rs displayed significant reductions in firing (**Figure 1D**; Wei et al., 2018). This is of interest given that the vHPC monosynaptically innervates NAc, especially the NAc shell. A recent report showed that roughly 35% of vHPC-NAc inputs were to D1R-containing MSNs within the NAc shell and 40% were to D2R-containing MSNs (Li et al., 2018). Given that HPC to NAc glutamatergic transmission is heightened following chronic alcohol exposure, it is reasonable that these inputs could be impacting the NAc in a cell-type-specific manner (Ji et al., 2017; Li et al., 2018). In the future, it would be interesting to examine vHPC-NAc circuitry to better understand if it is a primary contributor to the enhanced glutamatergic input on D1R-containing MSNs following chronic alcohol intake.

KETAMINE AS A POTENTIAL AUD TREATMENT OPTION

Clinical studies first demonstrated ketamine's therapeutic benefits by showing that slow infusions of sub-anesthetic ketamine (0.5 mg/kg over 40 min) alleviated depressive symptoms in patients suffering from TRD (Berman et al., 2000; Zarate et al., 2006). However, ketamine is a schedule III drug with great potential for abuse and dependence in humans (Narendran et al., 2005; Chang et al., 2016; Schak et al., 2016). Importantly, while ketamine has abuse potential, the low doses used clinically do not generally produce strong psychomimetic effects that may underly ketamine's rewarding properties (Zarate et al., 2006; Murrough et al., 2013). Furthermore, people suffering from AUD along with those who have a family history of AUD do not experience ketamine's psychomimetic effects to the same degree as healthy controls, suggesting low-dose ketamine carry a lower abuse potential among these individuals (Krystal et al., 2003; Petrakis et al., 2004). Preclinical studies demonstrated ketamine's potential therapeutic effects on alcohol intake by showing that acute, low-dose ketamine administration ($\leq$10 mg/kg, i.p.) attenuates alcohol intake in rats of both sexes (Sabino et al., 2013; Holleran et al., 2016; Rezvani et al., 2017, **Table 1**). Following these findings, a clinical trial was initiated to investigate the effect of repeated intermittent ketamine administration (0.5 mg/kg, i.v. over 40 min) in people suffering from AUD (Yoon et al., 2019; ClinicalTrials.gov, Identifier: NCT03658330).

While acute administration of ketamine at low doses may have a low potential for abuse, preclinical studies have demonstrated ketamine's abuse potential after chronic exposure by showing that rats display conditioned place preference and behavioral sensitization after repeated exposure ($\leq$10 mg/kg, i.p.; Strong et al., 2017; Schoepfer et al., 2019). Furthermore, rats will self-administer both low- and high-dose ketamine (De Luca and Badiani, 2011; Wright et al., 2017). Ketamine's dissociative effects have been shown to work primarily through NMDAR antagonism. In an early *ex vivo* study, a high concentration of

ketamine (100 μM) applied to cerebral cortex slices abolished action potential firing *ex vivo*, through blockade of NMDARs (Harrison and Simmonds, 1985). A more recent study showed that this same ketamine concentration, when applied to primary cortical neurons, led to elevated levels of intracellular Ca^{2+} release 10-min after application with effects sustained through 1-h (Zuo et al., 2017). Eventually, the sustained elevated levels of intracellular Ca^{2+} release following ketamine had apoptotic effects, suggesting that ketamine, at high concentrations, has excitotoxic effects (Zuo et al., 2017). However, the same report showed that a low concentration of ketamine (10 μM) did not induce the excitotoxic apoptotic effects observed with the high concentration, suggesting that exposure to higher doses of ketamine may induce secondary effects unrelated to its therapeutic effect (Zuo et al., 2017). Ketamine's antidepressant effect is exclusive to low doses (≤5 mg/kg, i.p.) in rodents since higher doses (≥20 mg/kg, i.p.) did not elicit an antidepressant response (Kim and Monteggia, 2020). Together, these studies show that ketamine as a therapeutic option might be safer and more efficacious at low doses, but this has been taken with caution as repeated and relatively higher doses of ketamine may have secondary effects contributing to excitotoxicity and abuse potential. It thus remains unclear whether repeated exposure to low-dose ketamine may induce neuroadaptations like those observed at higher concentrations. Therefore, this next section of the review will summarize what is known about neural mechanisms involved in mediating ketamine's therapeutic vs. its addictive properties.

Mechanisms of Ketamine's Effects

As described above, preclinical studies have shown that acute alcohol exposure leads to the inhibition of NMDA receptors (NMDARs), which bind the excitatory neurotransmitter, glutamate (Charness et al., 1988). Conversely, chronic alcohol exposure leads to increased potentiation of NMDARs, which contributes to LTP within reward-related brain regions (Dildy and Leslie, 1989; Renteria et al., 2017; Roberto and Varodayan, 2017). NMDAR-mediated induction of LTP following chronic alcohol intake is significant given that it has been shown to causally control alcohol-seeking behaviors measured during operant alcohol self-administration (Ma et al., 2018). Along these lines, human studies have shown an increase in the number of NMDARs in the brains of humans with AUD. An early study showed an increased density of NMDARs in the PFC, a brain region critically involved in reward signaling, of alcohol-dependent brains vs. controls (Freund and Anderson, 1996). More recently, postmortem human studies examining the brains of people with AUD compared to healthy controls showed increased mRNA expression of Grin2B, the gene encoding GluN2B subunit of the NMDAR, in both the PFC and hippocampus (HPC; Zhou et al., 2011; Farris and Mayfield, 2014). This is significant given that the presence of the GluN2B subunit enhances NMDAR channel function by increasing calcium (Ca^{2+})-permeability and, thus, promotes the formation of LTP through increased synaptic strengthening (Trepanier et al., 2012; Morisot and Ron, 2017). Altogether, these studies suggest that NMDARs may be prime targets for treating people with AUD.

Acute Ketamine Exposure

Preclinical studies examining acute, low-dose (≤10 mg/kg, i.p.) administration in rodents have shown that ketamine's antidepressant effects are mediated through NMDAR antagonism. An initial report showed that ketamine's antidepressant effects are associated with increased synthesis of brain-derived neurotrophic factor (BDNF), which required the inhibition of CaMKIII, also known as eukaryotic elongation factor 2 (eEF2) in the HPC (Autry et al., 2011). A follow-up study showed that eEF2 inactivation was a result of ketamine suppressing spontaneous NMDAR-mediated transmission in hippocampal slices, suggesting ketamine's antidepressant effects depend on NMDAR antagonism (Nosyreva et al., 2013). Here, it was further shown that after ketamine's suppression of NMDAR-mediated transmission ended, rapid synaptic potentiation associated with increased AMPAR insertion to the synapse occurred, implicating glutamatergic transmission as a primary target of ketamine (Nosyreva et al., 2013). However, a recent study suggested ketamine's antidepressant effects might be independent of its actions on NMDARs since hydroxynorketamine (HNK), a ketamine metabolite, exerted antidepressant effects independently of NMDARs (Zanos et al., 2016). In line with early reports, though, sustained potentiation of AMPARs was necessary for the antidepressant effects of HNK (Zanos et al., 2016). Another study however has shown that HNK does block NMDARs and that the dose of HNK used in Zanos et al. (2016) was insufficient to efficiently block NMDARs (Suzuki et al., 2000). While there is a controversy on the role of NMDA receptors in mediating ketamine's antidepressant effects, most studies agree that ketamine's antidepressant effects are mediated through potentiation of AMPA current in the hippocampus and PFC (Autry et al., 2011; Sarkar and Kabbaj, 2016; Zanos et al., 2016).

While ketamine impacts glutamatergic transmission directly in the HPC, these effects are indirect in the mPFC given that, here, ketamine acts directly on GABAergic transmission. Reports have implicated PFC GABAergic interneurons, specifically somatostatin-expressing (SST) interneurons, in controlling ketamine's antidepressant effects (Fuchs et al., 2017; Ali et al., 2020; Gerhard et al., 2020). Within the PFC, SST interneurons act as a microcircuit to provide inhibitory control over glutamatergic excitatory pyramidal neurons (Kepecs and Fischell, 2014). Interestingly, PFC SST interneurons are implicated in depression given that postmortem human studies showed reduced SST content in patients with depression (Sibille et al., 2011; Tripp et al., 2011; Seney et al., 2015). Furthermore, it has been shown that the disinhibition of PFC pyramidal neurons through knockdown of $GABA_A$ receptors on SST interneurons produced antidepressant and anxiolytic effects in mice, indicating that SST interneurons may be a prime target for antidepressant effects (Fuchs et al., 2017). A recent study used calcium (Ca^{2+}) imaging to show that ketamine inhibited SST interneurons in the mPFC, which led to the disinhibition of mPFC pyramidal neurons and enhanced glutamatergic transmission

(Ali et al., 2020). Importantly, two reports have shown that ketamine's effect on SST inhibition was through NMDAR antagonism since it was dependent upon the GluN2B subunit of the NMDAR (Ali et al., 2020; Gerhard et al., 2020). Blocking SST neurons in the PFC led to enhanced Ca^{2+} transients on PFC pyramidal neurons, suggesting that ketamine may exert NMDAR antagonism on inhibitory interneurons to disinhibit and induce synaptic potentiation within excitatory neurons (Ali et al., 2020). This is in agreeance with Fuchs et al. (2017) report showing that SST inhibition in mPFC produces antidepressant effects. Along these lines, studies have shown that acute ketamine administration activates the mTOR signaling pathway within the mPFC, which is associated with cell growth and survival, in male and female rodents (Li et al., 2010; Carrier and Kabbaj, 2013; Dossat et al., 2018). Activation of the mTOR signaling pathway was associated with increased expression of GluA1, Synapsin1, and PSD95, which are all protein markers highly correlated with dendritic spine number and/or head size, 2-h after ketamine with effects lasting up to 3-days (Li et al., 2010). Furthermore, dendritic spines within the mPFC increased following ketamine administration and one study showed that ketamine rescued stress-induced deficits in mPFC dendritic spines in male but not female rats (Li et al., 2010; Sarkar and Kabbaj, 2016). Taken together, ketamine likely disinhibits mPFC pyramidal neurons through blockade of NMDARs on SST interneurons, which increases the synaptic potentiation of pyramidal neurons by increasing mTOR pathway activation and induction of structural plasticity that may be behind the therapeutic effects of this drug.

It is worth noting that most studies mentioned above only investigated ketamine's antidepressant effects in male subjects. Several reports suggest an enhanced behavioral sensitivity to ketamine's antidepressant effects (Carrier and Kabbaj, 2013; Franceschelli et al., 2015; Sarkar and Kabbaj, 2016; Dossat et al., 2018). In the mPFC, mTOR phosphorylation was present in rats and mice of both sexes after ketamine administration, though females displayed this change at a lower dose of ketamine compared to males (Carrier and Kabbaj, 2013; Dossat et al., 2018). Similar changes were found with Akt activation in the mPFC, which occurred at a dose in female mice that were sub-threshold for males (Dossat et al., 2018). Given that phosphorylated Akt (p-Akt) can be modulated both by estrogen receptors along with BDNF-mediated activation of tyrosine kinase B (TrkB) receptors, these two receptor systems may play a synergistic role in the antidepressant effects of acute ketamine administration that would heighten sensitivity in females (Dossat et al., 2018). Furthermore, ketamine application to cultured induced pluripotent stem cell (iPSC)-derived astrocyte progenitors has been shown to bind estrogen receptor alpha (ERa) directly, and that estrogen and ketamine in combination produce additive effects on the induction of AMPAR expression (Ho et al., 2018). In line with this, ovariectomized female rats do not display antidepressant-like responses to acute ketamine administration until supplemented with estrogen and progesterone, suggesting a role for ovarian hormones in modulating ketamine's antidepressant effects (Carrier and Kabbaj, 2013). Similar findings with p-Akt were observed in the HPC along with elevated activation of CaMKIIα, which can promote the induction of plasticity through AMPAR trafficking to the synapse (Lu et al., 2010; Dossat et al., 2018). The sex differences described above may arise from a heightened sensitivity to ketamine's antidepressant effects in female rodents. Sex differences in ketamine metabolism have been described in a recent study that showed significantly greater levels of norketamine (NK) and dehydronorketamine (DHNK), ketamine metabolites, in the plasma of female rats as compared to males (Saland and Kabbaj, 2018). Furthermore, significantly greater concentrations of ketamine and NK were found in the PFC and HPC of female rats compared to males, indicating a slower clearance rate and longer half-life of ketamine in female rats (Saland and Kabbaj, 2018). Given that male and female subjects display sex differences in the neural mechanisms mediating ketamine's therapeutic properties, both male and female subjects must be taken into consideration when investigating the safety of ketamine as a therapeutic agent.

Furthermore, acute ketamine exposure may have rewarding effects. While acute ketamine impacts both glutamatergic and GABAergic neurotransmission to mediate antidepressant effects, it also affects the dopaminergic transmission, which is involved in mediating both its rewarding and potential addictive properties. A recent meta-analysis examining studies testing acute, low-dose ketamine's effect on dopamine release found significantly increased dopamine release in both mPFC and NAc of rodents following a single exposure (Kokkinou et al., 2018). As such, it is critical to understand how these neural mechanisms change following repeated ketamine exposure given that AUD patients would receive repeated infusions.

Chronic Ketamine Exposure

Behavioral studies show that repeated, low-dose ketamine administration induces sensitization to its locomotor activating effects in male and female rats (Strong et al., 2017; Schoepfer et al., 2019). Additionally, ketamine sensitization was associated with increased dendritic spine density in the NAc, suggesting the induction of structural plasticity alterations within a reward-related brain region in both sexes (Strong et al., 2017). Ketamine sensitization was also associated with elevated levels of ΔfosB in the NAc of both sexes (Strong et al., 2017; Schoepfer et al., 2019). The induction of ΔfosB and structural plasticity suggests enhanced glutamatergic transmission within the NAc following repeated ketamine exposure.

This increased excitatory neurotransmission within the NAc suggests a potential shift from acute NMDAR antagonism to chronic NMDAR potentiation following chronic ketamine administration, which is a similar observation to alcohol's mechanism of action. While it remains unknown how the shift from NMDAR antagonism to potentiation within the NAc might occur, there is some evidence that suggests it. Indeed, ketamine intravenous self-administration was associated with increased autophosphorylation of CaMKIIα in the NAc of male rats, specifically increased phosphorylation of CaMKIIα at the Thr286 site, which is associated with the induction of LTP and learning (Giese et al., 1998; Caffino et al., 2018). It is worth noting that a previous report examining cocaine's addictive effects showed that CaMKIIα

autophosphorylation in the NAc continuously increased ΔfosB expression and triggered CREB-mediated transcription (Robison et al., 2013).

Ketamine self-administration was also associated with elevated phosphorylation of the GluN2B subunit of the NMDAR in male rats, suggesting potentiation of this NMDAR subunit may also control ketamine's addictive properties (Caffino et al., 2018). Additionally, ketamine self-administration led to a reduction in BDNF and p-Akt within the NAc suggesting a potential reduction in NAc mTOR signaling in male rats (Caffino et al., 2016). Within the Akt pathway, phosphoinositide 3-kinase (PI3K) is upstream while mTOR is downstream and feedback loops exist such that mTOR can get indirectly turned on or off (Carracedo and Pandolfi, 2008). In a positive feedback loop, Akt activates nuclear factor kappa beta (NFκB) which turns off PI3K to stop mTOR activation and maintain cell health (Carracedo and Pandolfi, 2008). This is of interest given that a separate report revealed that a low concentration of ketamine (10 μM) application to cultured neurons led to the translocation of inactive NFκB in the cytoplasm to its active state in the nucleus following elevated levels of intracellular Ca^{2+} release (Wang et al., 2006). In the nucleus, activated NFκB triggers transcription and, recently, the ENCODE project revealed that transcription of the GluN2B subunit is NFκB-dependent (Xu and Lipsky, 2015). It is therefore plausible that ketamine-induced reductions in BDNF and p-Akt activation could explain increased GluN2B insertion within the NAc. Furthermore, ketamine sensitization was associated with increased GluA1 in the NAc of male and female rats, suggesting increased AMPAR insertion as well (Strong et al., 2017). Both the increased AMPAR expression and the GluN2B activation could explain a shift to NMDAR potentiation after repeated ketamine exposure, though future studies will need to confirm this. Importantly, alcohol's addictive properties are controlled by GluN2B activation on D1R-containing MSNs, indicating the mechanism by which alcohol and ketamine's rewarding properties are mediated might have some overlap (Cheng et al., 2017; Morisot and Ron, 2017).

To date, however, no studies have examined whether ketamine's addictive effects are controlled by D1R- or D2R-containing MSNs in reward-related brain regions, but pharmacological studies suggest that both D1Rs and D2Rs may play a role. For instance, acute ketamine administration has been shown to recruit both D1 and D2Rs given that intra-NAc D1R antagonism was abolished while D2R-antagonism attenuated ketamine-induced increases in locomotor movement (Matulewicz et al., 2010). Another report indicated that hippocampal evoked field potentials in the NAc were suppressed by ketamine and while D2R antagonism rescued these effects, D1R antagonism did not (Hunt et al., 2005). These findings should be taken lightly though, since pharmacological manipulations affect presynaptic NAc dopamine receptors as well, which are not cell-type specific.

Though evidence for a mechanism of action involved in controlling ketamine's addictive properties is limited, the currently available evidence highlights potential pathways involved. Like alcohol, repeated exposure to ketamine provides evidence of increased glutamatergic transmission based on increases in dendritic spines, ΔfosB expression, CaMKIIα autophosphorylation, and increased phosphorylation of the GluN2B subunit of the NMDAR. Additionally, ketamine may inhibit mTOR signaling given reduced BDNF and p-Akt in the NAc of male rats. Given that alcohol intake can be controlled by inhibiting mTOR in the NAc of male but not female mice, it is possible that if ketamine's therapeutic effects on alcohol intake involve mTOR that treatment for AUD would be more beneficial for male compared to female subjects. One study showed that ketamine-induced reductions in alcohol intake require mTOR signaling since rapamycin blocked these effects (Sabino et al., 2013).

As described above, ketamine induces a shift from NMDAR antagonism to potentiation of these receptors' function. One possible way this might occur could be through low dose ketamine antagonizing NMDAR located on GABA parvalbumin neurons within the mPFC, which disinhibit excitatory pyramidal neurons that directly project to the NAc (Ali et al., 2020). If enhanced excitation within the mPFC led to increased glutamate release within the NAc following repeated ketamine exposure, neuroadaptations could occur that parallel structural and synaptic alterations seen with other drugs of abuse. In general, alcohol and ketamine's mechanism of action overlap in many ways, and this calls into question whether repeated ketamine infusions should be used as a treatment for AUD. Furthermore, behavioral studies indicate female rats display enhanced sensitivity to ketamine's addictive effects, suggesting that ketamine's therapeutic dose may be different between the sexes (Strong et al., 2017, 2019; Wright et al., 2017, 2019; Schoepfer et al., 2019). Additionally, because mechanisms resulting from repeated ketamine exposure share similarities with those of alcohol, it is critical that more steps be taken in understanding the interaction between alcohol and ketamine before its use as an AUD treatment option in humans. However, repeated ketamine infusions for AUD patients may be administered safely if only a certain number of infusions are received. One report showed that four i.v. infusions of low-dose ketamine did not alter vulnerability to ketamine addiction, demonstrated by the fact that neither male nor female rats increased ketamine self-administration after receiving therapeutic infusions (Wright et al., 2019).

INTERACTIONS BETWEEN ALCOHOL AND KETAMINE

While several studies report on neural mechanisms contributing to both alcohol and ketamine's addictive and therapeutic effects, much less is known regarding how these two drugs interact. In a recent report, ketamine self-administration (0.5 mg/kg/infusion, i.v.) reduced alcohol intake in high-alcohol drinking male but not female rats, highlighting the critical need for sex to be more thoroughly examined as a factor before clinical testing of treatment options (Strong et al., 2019). The same study found that high-alcohol intake increased NAc dendritic spine density in both sexes, and while ketamine self-administration reduced these effects in males it did not

in female rats, suggesting that ketamine rescued the structural alterations in the NAc from alcohol in male but not female rats (Strong et al., 2019). It should be noted, though, that another study found that alcohol withdrawal reduced thin spine density in the NAc, though this could be due to differences in length of withdrawal and alcohol intake amount (Spiga et al., 2014). Interestingly, ketamine did not impact alcohol intake in low-alcohol drinking male rats and increased intake in low-alcohol intake female rats, indicating that individual differences in alcohol intake may also alter the response to ketamine (Strong et al., 2019).

Other studies have examined the effects of co-administration of alcohol with high doses of ketamine. In male rats, one study reported that co-administration of 20% alcohol with a high dose of ketamine (30 mg/kg, i.p.) increased VTA extracellular dopamine while ketamine on its own did not, suggesting that co-administering these drugs may amplify their rewarding properties (Zhang et al., 2018). Furthermore, tyrosine hydroxylase mRNA was increased with co-administration of alcohol and 30 mg/kg ketamine (Zhang et al., 2018). It has also been shown that co-administration of alcohol with a high concentration of ketamine (100 μM) amplified ketamine-induced apoptosis through heightened levels of intracellular Ca^{2+} (Zuo et al., 2017).

It should be noted, though, that in the clinic these two drugs will not be co-administered together since ketamine infusions will be administered to AUD patients abstinent from alcohol. Furthermore, the studies highlighted above examined high doses of ketamine while clinical studies are utilizing slow infusions of a low dose of ketamine (0.5 mg/kg, i.v. over 40 min; ClinicalTrials.gov, Identifier: NCT01558063). While no studies to date have examined the effect of repeated low dose ketamine administration on alcohol intake, a recent report showed that repeated, low-dose administration of ketamine (2.5 mg/kg, i.p.) attenuated alcohol-withdrawal induced depressive-like phenotypes in male rats (Getachew and Tizabi, 2019). Additionally, NBQX, an AMPAR antagonist, also attenuated alcohol-withdrawal induced depressive-like effects in rats, suggesting AMPARs blockade may have therapeutic benefits during alcohol withdrawal (Getachew and Tizabi, 2019). Together, these studies suggest that sex, individual differences, and the dose of ketamine can differentially alter the response to ketamine for AUD. Future studies should expand on sex and individual differences in AUD treatment response with repeated low-dose ketamine administration, and investigate neuroadaptations mediating ketamine's therapeutic effects for AUD to better understand the safety of its use in both male and female subjects.

CONCLUSION

Several reports indicate that repeated exposure to alcohol increases glutamatergic transmission through NMDAR potentiation in reward-related brain regions such as the NAc and DMS. Ketamine is being investigated as a potential treatment option given that, acutely, it acts as an NMDAR antagonist (ClinicalTrials.gov, Identifier: NCT01558063). However, given that AUD is a chronic relapsing disorder, multiple ketamine infusions are necessary to maintain sobriety. After repeated exposure, ketamine appears to also potentiate NMDARs, calling into question the safety of its use as an AUD treatment option. Furthermore, most studies have only investigated these effects in male subjects, and a recent study suggests that repeated ketamine exposure may not reduce alcohol intake in female rats the same way it does in male rats (Strong et al., 2019). Interestingly, though, the R-ketamine enantiomer has shown some therapeutic potential as a treatment for opioid use disorder in rats given that it blocked morphine-induced conditioned place preference and alleviated withdrawal symptoms (Witkin et al., 2020). While the evidence presented in this review suggests that repeated ketamine treatment for AUD may put patients at further risk for addiction-like behaviors, future studies should tease apart effects of S- vs. R-ketamine enantiomers as well as differences in males vs. females. Additionally, no studies to date have examined ketamine as a treatment option for adolescents suffering from AUD, a group comprised of around 400,000 individuals (National Institute on Alcohol Abuse and Alcoholism, 2018). This is extremely important given that adolescence is a period when drug abuse often starts and because ketamine's therapeutic effects are exerted through mechanisms in the mPFC, which is not fully developed until adulthood (Arain et al., 2013). As such, more work is necessary for both sexes to understand the neuroadaptations occurring after repeated ketamine infusions for chronic alcohol use.

AUTHOR CONTRIBUTIONS

CS wrote the first draft of this review and then MK and CS worked together to edit it. All authors contributed to the article and approved the submitted version.

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REVIEW
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Resilience: Safety in the Aftermath of Traumatic Stressor Experiences

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The relationship between adverse experiences and the emergence of pathology has often focused on characteristics of the stressor or of the individual (stressor appraisals, coping strategies). These features are thought to influence multiple biological processes that favor the development of mental and physical illnesses. Less often has attention focused on the aftermath of traumatic experiences, and the importance of safety and reassurance that is necessary for longer-term well-being. In some cases (e.g., post-traumatic stress disorder) this may be reflected by a failure of fear extinction, whereas in other instances (e.g., historical trauma), the uncertainty about the future might foster continued anxiety. In essence, the question becomes one of how individuals attain feelings of safety when it is fully understood that the world is not necessarily a safe place, uncertainties abound, and feelings of agency are often illusory. We consider how individuals acquire resilience in the aftermath of traumatic and chronic stressors. In this respect, we review characteristics of stressors that may trigger particular biological and behavioral coping responses, as well as factors that undermine their efficacy. To this end, we explore stressor dynamics and social processes that foster resilience in response to specific traumatic, chronic, and uncontrollable stressor contexts (intimate partner abuse; refugee migration; collective historical trauma). We point to resilience factors that may comprise neurobiological changes, such as those related to various stressor-provoked hormones, neurotrophins, inflammatory immune, microbial, and epigenetic processes. These behavioral and biological stress responses may influence, and be influenced by, feelings of safety that come about through relationships with others, spiritual and place-based connections.

Keywords: resilience, traumatic stressors, biopsychosocial, safety net, post-trauma, social connection, spirituality, nature

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INTRODUCTION

Research concerning the impacts of stressors has long focused on determining underlying biopsychosocial processes and how these might give rise to various psychological and physical pathologies. Numerous experiential and individual difference factors (e.g., gender, ethnoracial status, age, earlier stressor encounters) that could exacerbate or diminish the actions of stressors have been established (Anisman et al., 2018). Likewise, genetic and epigenetic factors that code for particular biological features (e.g., processes related to glucocorticoid or neurotrophin functioning) are tied to the occurrence of behavioral and physical disturbances (Suri et al., 2013; Szyf et al., 2016; Mehta et al., 2020), and glucocorticoids influence epigenetic responses to stress (Reul et al., 2014).

These actions are further affected by the type and timing of stressor challenges (Burns et al., 2018; Torres-Berrío et al., 2019). However, there are so many experiential and biological (hormonal, neurochemical, growth factor, and inflammatory) changes associated with stressful events that it may be impractical to assign a given process to any particular pathology. Instead, it may be more productive to identify *signatures* that comprise a constellation of factors (much as in a precision medicine approach) that might account for specific features of various pathologies, and vulnerability or resilience regarding their development and progression.

Figure 1 provides a broad overview of factors that contribute to resilience over the course of the stressor experience and in its aftermath. In this regard, we focus on several pre-disposing elements that shape responses to stressors. Such responses vary as function of both the objective characteristics and subjective appraisals of the stressor, which can interact with emotional, behavioral, and biological responses. Furthermore, following termination of a stressor, a series of adaptive changes can occur that might favor resilience and well-being, but failing these changes, vulnerability to pathology may be exacerbated. Finally, much like predisposing factors that shape stress processes during ongoing challenges, psychosocial resources may serve to re-establish safety and security that can contribute to sustained resilience to the impacts of previously experienced stressors, as well as those that might be encountered in the future.

Understandings of both vulnerability and resilience often adopt a linear approach to the phases of responding to a stressor, while at the same time acknowledging that such processes are multidimensional, synergistic, and reciprocal. We were tempted to review the literature in much the same manner. Instead, to better illustrate the interplay of features, we have opted to convey a few key elements that might contribute to resilience by framing them within the context of specific stressor scenarios. These scenarios are based on some areas of research in which we have been actively engaged to understand stress dynamics, namely (1) psychological abuse in an intimate relationship, (2) the experience of refugees to Canada, and (3) intergenerational trauma among Indigenous Peoples as a result of the Indian Residential School system. Through these scenarios, we provide fundamental information regarding central biopsychosocial aspects of resilience and vulnerability. In so doing, we emphasize the factors that contribute to the creation of safe spaces that enable individuals or groups to grow and thrive. In presenting each of these scenarios, we opted to consider a limited number of resilience factors relevant to them, but we underscore at this point that many of the components that contribute to resilience in any given scenario are also applicable to the other stressor situations.

RESILIENCE

Before considering the factors that favor resilience, we provide a broad overview of what resilience is often thought to entail, including several elements that have received less attention even though these may have fundamental repercussions to well-being. Resilience may reflect the propensity of an individual to overcome an illness, or it can refer to the ability of an individual to withstand the effects of stressful events that would ordinarily lead to pathology. Resilience may also entail a process of adjustment, transformation, and even growth (Ungar, 2008; Allen et al., 2014). Furthermore, although vulnerability and resilience are frequently considered to sit at opposite ends of a continuum, this is not fully accurate. An individual who is vulnerable to illness owing to the presence of certain genes or particular stressful experiences, might also be endowed with other genes or have had experiences that enable them to act against such risk factors. Likewise, the presence of a supportive social relationship, or having particular coping skills may allow individuals at risk to endure stressful events, thereby mitigating illness.

On the flip side, a person may be bestowed with numerous protective characteristics that favor resilience to diverse challenges, but there may be one simple feature that renders ineffective other protective factors in response to a given challenge. By example, the presence of a gene mutation that causes cancer development may override other factors that might ordinarily contribute to resilience. This said, to a considerable extent, understanding what makes individuals vulnerable to the negative impacts of stressors might also inform the processes that foster resilience. This includes individuals' subjective interpretations of events, their emotional reactions, the resources and skills they have available to cope with the event, and biological alterations that underpin vulnerability or resistance to illness. In effect, the search for features of the situation, or of the individual, that increase vulnerability to behavioral or physical disturbances revealed several factors that fostered resilience.

In response to common stressors encountered on a day-to-day basis, individuals' behavioral coping methods and stress-relevant biological systems ought to operate sufficiently well so that the risk of pathology emerging is low. As stressor severity increases, especially if it is uncontrollable, unpredictable, and experienced chronically or repeatedly, the load placed on biological systems increases commensurately. Among some individuals, the combination of effective protective behavioral and neurobiological processes may promote resilience, even in the face of multiple risk factors. In others, however, the continued strain may undermine behavioral coping methods so that greater pressure is placed on biological defense systems. Ultimately, a weak link in a component of such a system may give way, culminating in the emergence of a particular pathology. For one person this might comprise the provocation of diminished immune responses, and hence the emergence of related diseases. For another it may involve a cardiovascular disturbance that develops owing to chronic inflammation, or it might entail changes of neuroplasticity that promote psychological disorders, such as chronic anxiety, depressive disorders, or posttraumatic stress disorder (PTSD). Moreover, even when an individual appears to be resilient in the face of a stressor owing to a specific neurobiological process, this does not necessarily imply that this will hold in the long run. For example, short term inflammatory changes might be adaptive under certain conditions, but if these persist for extended periods, they may have multiple adverse

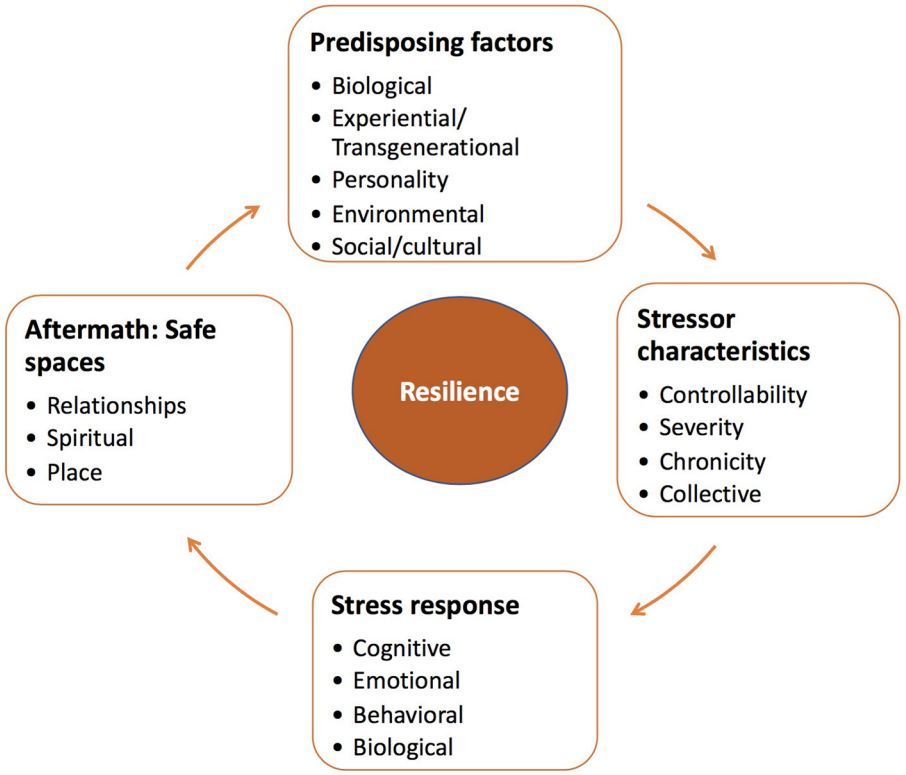

FIGURE 1 | Resilience is regarded as a process that entails the dynamic and reciprocal relationships between features of the individual and their environment that influence (and are potentially triggered by) particular characteristics of the stressor and its appraisal. These appraisals may give rise to various responses to contend with the stressor (which might alter the stressor or bring about other stressors or protective factors). In the aftermath of stressor events, resilience might be fostered as a function of resources and processes that bring about feelings of safety and reassurance.

actions, promoting depression, metabolic syndrome, type 2 diabetes, and heart disease (Mastorci et al., 2009; Anisman et al., 2018; Burgueño et al., 2020). By the same token, some behavioral coping strategies (e.g., avoidant coping) might be effective in the short term but could potentially undermine the adoption of strategies (e.g., obtaining help) that are needed to contend effectively with the stressor in the longer term.

With this said, it should be asked whether there are general features of individuals or particular experiences that favor resilience? For example, it has frequently been maintained that positive and nurturing early life experiences may act in this capacity by affecting neuronal plasticity or changes in gut microbiota (Kentner et al., 2019), and might even prime biological systems such that later challenges will be met by moderate neurochemical changes that enhance coping abilities (Anisman et al., 2018). At the same time, encountering stressful events that are experienced as tolerable could potentially facilitate learning how to appraise and cope with subsequently encountered challenges (McEwen, 2020). In effect, resilience is not a generalized state of the individual, but instead comprises multiple adaptations that might occur in response to challenges encountered within several domains and over time.

More commonly, resilience was attributed to a constellation of processes that reflect positive worldviews, such as altruism, social bonding, adaptive social behaviors, and appropriate responses to fear-related situations (Charney, 2004), perhaps owing to variations of oxytocin, operating in conjunction with dopamine variations within the nucleus accumbens (McQuaid et al., 2014). Relatedly, resilience might entail the ability to adhere to a positive perspective on life, eudaimonia (happiness or flourishing), accepting change, maintaining control, spirituality, as well as particular cognitive abilities, such as being adaptable and flexible in response to challenges (Belsky and Pluess, 2013; Gabrys et al., 2018). Certain personality dimensions may likewise contribute to resilience, including high levels of self-esteem, self-efficacy, mastery, optimism, extraversion, self-empowerment, hardiness, hope, and an internal locus of control (e.g., Carver and Connor-Smith, 2010; Jeste et al., 2015). Resilience has also been tied to having a strong social identity, being positively connected to others, and having an effective social support network (Haslam et al., 2014, 2016). In this regard, socio-ecological frameworks for understanding resilience have emphasized culture, spirituality, intergenerational relationships, and connections to the land (Kirmayer et al., 2011; Toombs et al., 2016). In essence, resilience emerges as a relational process involving the interplay of individual, social, cultural, and environmental factors (Liebenberg et al., 2015). Thus, beyond the outcomes ordinarily attributed to resilience, it has been

maintained that it is as much a social process as it is an outcome (Norris et al., 2008).

Also entering the mix are multiple neurobiological elements, including numerous genetic factors that code for specific processes (e.g., neuropeptide Y or particular neurotrophins) and particular epigenetic changes may similarly imbue individuals with greater resilience (e.g., La Greca et al., 2013; Schmeltzer et al., 2016). These epigenetic changes could result in enhanced immune or endocrine functioning that are essential for adaptation (Mehta et al., 2020). Similarly, while some inflammatory processes have been associated with varied illnesses, epigenetic changes can act against cytokine-mediated inflammation and might thereby protect against stressor-related psychological and physical disturbances (e.g., Wang et al., 2018). Likewise, other stress-related hormonal factors (e.g., corticotropin releasing hormone, vasopressin, oxytocin, natriuretic hormones, angiotensin, neuregulins, some purinergic substances, and especially inflammatory factors) might be fundamental in accounting for the development of, or resilience related to comorbidities that are frequently apparent between stress-related psychological conditions and the appearance of metabolic syndrome, type 2 diabetes, and coronary artery disease (e.g., Zapata-Martín Del Campo et al., 2018).

STRESSOR CHARACTERISTICS AND APPRAISALS

There are certain features of stressor events that may be more or less likely to create adverse outcomes. Ordinarily, severe stressors are more likely to favor pathology than are mild challenges. As a result, it might be thought that physical assault of one's intimate partner is more serious than psychological aggression. It might be expected that fleeing ethnic genocide would have greater pathological repercussions than encountering day-to-day discrimination in the country in which refuge was obtained. Or that the trauma and abuse experienced directly by survivors of the Indian Residential School system would be greater than the transgenerational trauma experienced by descendants. Yet in all of these instances, while the obviously severe traumas are unquestionably stressful, experiences with milder ongoing stressors were also found to be strongly linked to subsequent psychological disturbances (e.g., Matheson et al., 2007; Jorden et al., 2009; Bombay et al., 2014, 2019; Arriaga and Schkeryantz, 2015). In effect, to a considerable degree, the impact of stressors is determined by subjective appraisals of the experience, which may vary on the basis of the context in which they were experienced, as well as on the basis of earlier trauma encounters. As a result, consideration of objective features of a stressor is intricately connected to subjective appraisals.

In response to a potential stressor, individuals appraise whether the stimulus represents a threat. This is followed by a secondary appraisal concerning their belief that they have the capacity to deal with it effectively (Lazarus and Folkman, 1984). The appraisals that individuals make might be influenced by previous experiences in dealing with both similar and dissimilar challenges, or they may stem from specific beliefs, self-perceived abilities, as well as personality differences (Anisman and Matheson, 2005). When appraisals reflect threat of harm or loss, negative emotions such as anxiety or anger will ensue, whereas appraisals that frame the stimulus as a challenge or as an opportunity might elicit positive, motivating emotions.

Of particular relevance to this review is the importance of events that transpire after a stressful event has ended, and the implications for biological processes that underpin the onset of stress-related pathologies. Following a stressful experience, it is important that biological systems normalize relatively quickly. Aside from the unnecessary use of critical resources, a sustained neurobiological stress response may give rise to brain neuronal and peripheral processes operating excessively, which could lead to adverse outcomes (McEwen, 2007). In rodents, upon termination of an aversive event, stress-related neuronal activity may persist as long as the animal remains in the stress environment. Yet, this forced exposure may result in extinction of the stress response, including alterations of stress-related neurochemicals in rodents (Stockhorst and Antov, 2016), just as it does in humans treated through exposure therapy to diminish symptoms of anxiety related to specific cues, as in the case of phobias (Foa and McLean, 2016). It may be particularly significant from a resilience perspective that in an animal stress paradigm, normalization of the stress response can be promoted through the introduction of a safety signal (Minor et al., 1990), which might have its effects through actions at the insular cortex (Christianson et al., 2008) that subserves multiple functions, such as decision-making, risk prediction, and complex social behaviors (Gogolla, 2017). It appears that some brain regions operate in response to the here and now, whereas others also influence future responses to stressors.

Feelings of safety may be fundamental in turning off the stress response. Failure to achieve feelings of safety, possibly owing to dysfunction of neuronal circuits that permit feelings of danger to abate, has been associated with the development of anxiety-related disorders (Szechtman et al., 2020). When a stressor situation is one that does not permit feelings of safety to emerge, the activity of the anterior insula and amygdala are elevated (Tanovic et al., 2018). The elevated neuronal activity at these sites may reflect continued efforts by the brain to make sense of the situation. It has indeed been suggested that safety may be a learned response that fosters feelings of security and protection, but if safety is not established features of pathology (e.g., hypervigilance associated with PTSD) may evolve (Kong et al., 2014).

Similarly, it is fairly well established that having a negative ruminative coping style may be tied to later development of depressive disorders (Nolen-Hoeksema, 1998), and angry rumination has been associated with cardiovascular reactivity (Busch et al., 2017). In a sense, ruminating over a past event reflects an inability to 'let go' and in this way might have carry-over consequences that are not unlike those that accompany a persistent sense of being unsafe upon stressor termination. Negative rumination and worry represent the mind never coming to rest, and not having the opportunity to recuperate (Yan et al., 2013).

In the subsequent sections of this review, we will provide a series of scenarios that allow us to elucidate key appraisal processes that give rise to particular behavioral and biological coping responses. Such responses may directly influence stress-related outcomes. However, resilience to these outcomes, and indeed, psychological growth may ensue when individuals or members of a threatened group are able to cultivate cognitive, emotional, or physical safe spaces. Various strategies for achieving safety in the aftermath of differing stressor experiences will be considered.

SCENARIO 1. PSYCHOLOGICAL ABUSE IN AN INTIMATE RELATIONSHIP

Psychological abuse frequently occurs within heterosexual dating relationships, as well as within the family home. While less visible than physical abuse, the effects of psychological abuse appear to be insidious with substantial impacts on the well-being of the victim. Although the perpetrator and target of such abuse cross gender lines, male partners are more commonly the aggressor, and women the target (Heise et al., 2019). Critical aspects of intimate partner abuse are that it represents a betrayal of the person who is supposed to be a trusted source of support and affirmation, undermines the victim's beliefs in her own worth and place in the world, and creates a home environment that is no longer a safe haven. Some women find the strength to terminate their abusive relationships, to transition from a life of being controlled to being in control, and to be resilient to the potential long-term impacts on stressor-induced outcomes, including depression, anxiety, substance use, or PTSD (Anderson et al., 2012).

Stressor Controllability

Among those who have not experienced psychological abuse, there may be a tendency to underestimate the power of the persistent and repeated insults, passive aggression, and gaslighting on the victim's confidence, feelings of agency, and ability to take control of her situation. Psychological abuse is about the perpetrators' need for control and dominance, and the subjugation of their female partner (Ubillos-Landa et al., 2020). As described earlier, of the various features of a stressor situation that favor behavioral disturbances, control over the stressor has been most widely studied (Maier and Seligman, 2016; Anisman et al., 2018). Many of the features of psychological abuse inherently undermine women's appraisals of control, including its unpredictability, volatility, uncertainty ("is that really what he meant"), ambiguity ("did I do something to deserve it"), and complexity ("does he despise me or love me").

Typically, uncontrollable events are more likely to promote behavioral disturbances than are controllable stressors. Some theorists attributed these variations to cognitive changes (e.g., learned helplessness), whereas others attributed these outcomes to particular stress-related neurochemical alterations (e.g., norepinephrine activity in the prefrontal cortex, dopamine in the nucleus accumbens) (Anisman et al., 2018). Relative to controllable stressors exposure to an identical uncontrollable stressor regimen in rodents resulted in greater turnover of norepinephrine and serotonin functioning across several brain regions, such as medial prefrontal cortex, hippocampus, amygdala, and hypothalamus, varying between strains of mice (Kasabov et al., 2019). The uncontrollable stressor regimen induced a reduction in the levels of norepinephrine and serotonin, possibly reflecting utilization of these amines exceeding their synthesis (Anisman et al., 2018). Furthermore, stressors promote brain region-specific variations of several neurotrophins, such as brain-derived neurotrophic factor (BDNF) that may be relevant to disorders such as depression (Duman and Li, 2012). It is of particular interest that although stressors generally reduce hippocampal BDNF, expression of BDNF was increased within the anterior cingulate, more so in response to a controllable rather than an uncontrollable stressor. The greater effects of the controllable stressor in this instance might reflect the adoption of active coping efforts, or to learning about the controllability of the stressful situation (Bland et al., 2007). In recent years, many of the learned helplessness advocates have come around to recognize the neurochemical underpinnings of the behavioral disturbances and have offered their own views regarding the specific neurobiological processes that contribute to behavioral disturbances (Maier, 2015). This has included variations of BDNF, as well as serotonergic changes. In this context, not only do controllable and uncontrollable stressors differentially influence serotonin functioning, but it also appeared that rodents that had encountered a controllable stressor did not exhibit the behavioral disturbances and serotonergic changes ordinarily associated with a subsequent uncontrollable stressor experience (Amat et al., 2010). In essence, learning that a stressful situation is controllable may immunize the organism against subsequent adverse effects that stem from a subsequent uncontrollable stressor.

Relatedly, from a resilience perspective, the physiological (and subsequent behavioral) impacts that occur in humans can be influenced by previous experiences with controllable stressors. If women who experience abuse have learned safety strategies for contending with mild interpersonal challenges in their current or previous relationships (e.g., possibly confronting the insults, or by turning to others who re-affirm her self-esteem), they might be able to manage or terminate the relationship if the abuse continues (Wood et al., 2019). Ordinarily, when a challenge first occurs, in the absence of previous relevant experiences, it may be unclear whether the stressor is controllable or uncontrollable, or whether it will be a brief insult or one that will be prolonged or repeated. Indeed, this is often the case with abuse, as it might start in small ways that can initially be ignored but evolves over time, as women increasingly question their own worth in response to repeated challenges. But in the first instance, some neurobiological changes ought to occur rapidly and relatively strongly, and then, once the characteristics of the stressor are understood, these responses could be down- or up-regulated as necessary to contend with it effectively. Thus, hormones, such as hypothalamic corticotrophin releasing hormone, pituitary adrenocorticotropic hormone (ACTH), and adrenal cortisol (corticosterone in rodents) ought to respond quickly, and hence, might initially be less influenced by stressor

controllability, relative to several neurotransmitters (Anisman and Matheson, 2005). As well, as described earlier, within the anterior cingulate cortex, which is involved in the processing of emotionally salient events as well as in decision making, BDNF expression was elevated to a greater extent after controllable rather than uncontrollable stressors (Bland et al., 2007). This may reflect the possibility that BDNF was in some fashion related to new learning associated with a controllable situation rather than being a consequence of the stressor itself. Thus, it is tempting to suggest that learned controllability contributes to resilience, but at times such a response might be counterproductive as this view is predicated on the assumption that appraisals of controllability are actually accurate. As we know, humans may not be accurate in their appraisals and in decision making (Tversky and Kahneman, 1974). If controllable events are appraised as being uncontrollable, individuals may cease making efforts to determine their own destinies (as is too often the case among women in abusive relationships), they may seek exceedingly complex solutions to contend with these events, or they might adopt counter-productive strategies (e.g., substance use). Conversely, if uncontrollable events are appraised as controllable, then individuals may persist in fruitless efforts to alter the situation (e.g., repeatedly excusing or forgiving the abusive behavior; Ysseldyk et al., 2009).

Behavioral Coping Strategies

Based on the appraisals (or misappraisals) that are made, specific coping strategies will be endorsed, although to an extent these coping methods may also reflect past experiences and dispositional propensities (i.e., coping styles). If individuals are able to enlist effective methods of coping, stressor-related problems ought to be relatively limited. In contrast, adopting poor coping methods that do not effectively manage the stressor or the emotions it elicits may favor the development of pathological conditions.

A wide range of coping strategies can be used to deal with stressors. These are often viewed as falling into three broad categories: problem-solving, emotional expression, and avoidance. Although specific coping behaviors are often assigned to one category or another, in fact, most coping methods do not fall exclusively within a single category. Instead, particular behaviors can serve in multiple capacities, varying with the nature of the stressor, the context in which it is encountered, and over the course of time (Anisman and Matheson, 2005). For example, a woman in an abusive situation might seek social support in order to obtain information that allows her to determine how to effectively manage or leave her situation, or she might seek support in order to avoid thinking about the abusive circumstances she experiences at home. Thus, although in both instances, women are seeking support, the purpose differs.

It should be underscored that particular coping behaviors are not typically used in isolation of other strategies. It may be that adeptness in appropriately using several coping strategies in conjunction with one another is most likely to promote resilience. For instance, rumination that is accompanied by self-blame, recrimination, and emotional expression, may favor the occurrence of depression (Nolen-Hoeksema, 1998), as well as PTSD (Spinhoven et al., 2015). Unfortunately, this pattern characterizes the coping profile often endorsed by women experiencing psychological abuse (Matheson et al., 2007). Conversely, rumination accompanied by problem-solving and strategies to manage emotions, as well as cognitive disengagement is not predictive of depression (Kelly et al., 2007). Being skilled at using a relatively broad range of coping strategies, and flexible in the choice of behaviors, so that the individual is able to shift from one strategy to another as the situation requires, may be the ideal approach to deal with stressors (Cheng et al., 2014; Juster et al., 2016). Being flexible in appraising stressors may similarly be advantageous (e.g., recognizing when a situation is controllable and when it is not), and may contribute to effective coping (Gabrys et al., 2018).

A common incorrect assumption is that emotionally expressive coping is a maladaptive strategy, given that it is often associated with depressive disorders. Yet, emotional expression may be instrumental in acknowledging, exploring, and understanding emotional responses to challenges, and may be fundamental in helping individuals come to terms with their feelings, consequently diminishing distress (Austenfeld and Stanton, 2004). Particularly when the stressor is uncontrollable, strategies that enable the individual to manage their emotional reactions might indeed be the best way to contend with the situation. In this regard, women's use of emotionally expressive coping strategies might signal a request for help from others in her support network. Conversely, emotionally avoidant coping among women in abusive situations can provide them with some degree of illusory control, at least in the moment (Matheson et al., 2007). In actuality, there is no single strategy that is best to deal with stressors across all situations, and instead coping methods ought to vary with the nature of the stressor and the context in which it is experienced.

Relationships and the Social Safety Net

The extremely detrimental effects of experiencing abuse from an intimate partner (exacerbated by the isolation from others that is often imposed by abusive partners) is testament to the importance of social connections for well-being. Strong and supportive social relationships are a fundamental protective factor contributing to stressor recovery and resilience (Hobfoll et al., 2007; de Terte et al., 2014; Karmel et al., 2020), including in the aftermath of intimate partner abuse (Anderson et al., 2012). The nature of such relationships might vary in importance over the life span, shifting, for example, from familial caregivers (e.g., parents), to peers, to intimate partners and spouses, and to offspring (Wrzus et al., 2013). In this regard, it has been suggested that it is not simply the number of people within a support network that is important, but rather, the perceived availability of an appropriate source of support that is matched to the stressor at hand (Cutrona and Russell, 1990; Rini and Dunkel Schetter, 2010). Such matching refers to the support person's capacity to provide the type of support needed in response to a given situation, which might range from emotional reassurance (e.g., from a close friend) to having the skills or knowledge to help address the problem (e.g., a helping professional).

While perceptions of support availability are critical to providing the individual with the confidence and assurance that they can contend with a stressor, the actual receipt of support is less consistently associated with positive well-being outcomes (Uchino et al., 2011; Guilaran et al., 2018). Enacted support carries a complex set of implications, ranging from indebtedness, to its effects on perceived self-efficacy, to say nothing of its responsiveness to the problem at hand, and the erosion of support that can occur over time (Maisel and Gable, 2009; Ren et al., 2018; Ross et al., 2020). Such erosion is not an uncommon experience among women in abusive relationships. Sources of support become increasingly fatigued and frustrated by her inability to terminate the relationship, and less willing to provide support over time (Waldrop and Resick, 2004; Anderson et al., 2012). As a result, women in abusive relationships are less likely to reach out, and friends and family are uncertain how to respond when they do (Zautra, 2014).

In this regard, social support seeking can be a double-edged sword. When the individual turns to a person from whom they anticipated support, an unsupportive response can be highly distressing (Jorden et al., 2009; Woods et al., 2020). Such unsupportive interactions might exacerbate engagement in ineffective coping strategies (e.g., self-blame), and undermine perceptions of a supportive social safety net that had been counted upon (Manne et al., 2019). Much like appraisals and coping processes, for a social safety net to be effective, there needs to be flexibility within the support system. This serves both to ensure appropriate support for the specific stressor, as well the ability to identify an alternative source of support when a key resource falls through (as in an abusive relationship) (Laireiter et al., 1997).

Perhaps for this reason, and particularly given that humans are the 'ultra-social animal' (Tomasello, 2014), being imbedded within a relevant social group (Kaniasty and Norris, 2009; Uchino et al., 2018), or having a sense of belonging to multiple social groups affords benefits to well-being (Haslam et al., 2009). Multiple groups (e.g., sports teams, family, work colleagues, church members, home community) likely reflect different social functions, and as a result, the more groups that an individual identifies with, the more resilient they appear to be in the face of personal, social, and physical stressors (Iyer et al., 2009; Jetten et al., 2015). Even when an individual's group identity is threatened (e.g., through stigma, discrimination, or political violence), which ought to result in numerous negative psychological and physiological stress responses (Matheson and Anisman, 2012), highly identified individuals often experience the least distress (Cruwys et al., 2014). Perhaps emanating from evolutionary advantages (Tomasello, 2014), the groups to which a person belongs provide key social and tangible resources that enable individuals to accomplish goals, including social change through political action, which would otherwise be unattainable at the individual level (Haslam et al., 2009). In addition, belonging to multiple groups provides the flexibility needed to address various stressors, along with the capacity to turn to any one of multiple people within the support system (Haslam et al., 2016), or to create an identity segue to draw on new groups following a life transition (Ysseldyk et al., 2013). For all of these reasons, the multiple benefits of social identification and connectedness has been referred to as the "social cure" (Jetten et al., 2017).

Although the perceived availability of at least one trusted source of support appeared to be the most important factor associated with resilience among women leaving an abusive relationship, identifying such support after the prolonged restrictions associated with experiencing a controlling abusive partner might be a challenge. Despite the erosion of support women experienced while in the relationship, those who were resilient in the aftermath found that informal networks (e.g., family) were willing to re-engage once they had left the abusive partner (Anderson et al., 2012). Other sources of support exist within the community, including peer supports. Indeed, once women have re-established their lives, peer support and volunteering can be an effective strategy not only for building a social safety net, but can often promote the ability to find self-acceptance and meaning in the abusive experiences, which further contribute to long-term resilience and well-being (Zautra, 2014).

While social safety nets are most often considered in relation to human social supports, there is mounting evidence that supportive relationships can be in the form of companion pets or service animals. Just as many women in an abusive situation may feel unable to leave due to concerns about her children, they may also be unwilling to leave behind a beloved pet that might not be welcome in transitional housing (Barrett et al., 2018; Stevenson et al., 2018). Owning a pet is associated with positive benefits, such as helping the individual maintain a positive self-image, increasing quality of life, reducing anxiety, or hyperarousal associated with PTSD, or even providing a basis for strengthening human social connections through social participation (Wood et al., 2015; Brooks et al., 2018; Wells, 2019). Companion animals might be especially important sources of support and safety for those populations who are socially marginalized (Brooks et al., 2016, 2018), as animals are perceived as non-judgmental, providing unconditional acceptance that may be lacking in more traditional relationships (Brooks et al., 2016). For example, among homeless youth, having a companion pet helped mitigate the stressors associated with street life, reduced youths' engagement in risky behaviors (e.g., substance use), provided them with a safe and secure attachment figure, and gave youth the opportunity to experience the compassionate side of humanity (Lem, 2016). Homeless women in particular (many of whom have experienced previous abuse) recognized the therapeutic value of pets in providing them with companionship, unconditional acceptance, and a sense of personal safety (Labrecque and Walsh, 2011). War veterans experiencing PTSD symptoms also benefitted from service dogs trained to meet their psychological needs (Beetz et al., 2019), not only providing them with an ongoing sense of reassurance and safety, but in addition resulting in a decrease of PTSD symptoms over time (Kloep et al., 2017; O'Haire and Rodriguez, 2018), as well as co-occuring problematic substance use (Husband et al., 2020). Although there is still a need for evidence-based research to fully understand the effects of animal-assisted interventions (Fine et al., 2019), having a pet appears to provide the individual with two fundamental

factors associated with resilience, namely a secure connection and greater feelings of safety (Zilcha-Mano et al., 2011).

SCENARIO 2. THE REFUGEE EXPERIENCE

In the face of violent national ethnic or religious genocides, citizens flee their home countries to seek refuge in receptive nations. Many refugees have experienced the death of loved ones, been subjected to torture, witnessed the violent apprehension of family members, friends and neighbors, survived horrendous conditions in refugee marches and camps, and feared for their own and their family's survival. Once established in a host country, refugees must often learn a new language, a new set of cultural and social norms, find employment and housing, and sometimes continue to worry about family members who were unable to escape; those who belong to a racialized group may also encounter negative stereotypes and discrimination. In effect, the refugee experience is one of social and physical displacement and turmoil. While such severe and ongoing stressors are often associated with a range of stress-related pathologies, many refugees not only survive the experience, but flourish and create a new life for themselves and their families and make strong contributions to their new home communities.

Notably, just as for women in abusive relationships, refugees' appraisals of control over their situation may contribute to their resilience upon resettlement. The capacity to enact behaviors to establish themselves in a new country (e.g., learning a new language) might contribute to such perceptions of control. In contrast, other experiences, such encounters with continued discrimination could engender feelings of uncontrollability, and in addition challenge perceptions of the supports available to build a new life (Jorden et al., 2009). Perhaps for this reason, the creation of community social networks that decrease refugees' feelings of isolation and increase feelings of empowerment play an important role in their capacity to adapt to a new setting and to demonstrate resilience in the face of subsequent stressors (Block et al., 2018).

Sensitization of Neurobiological Processes

Despite having physically left behind an unimaginably traumatic situation, memories and emotions associated with their past experiences continue to have a presence in the lives of refugees. An important feature of stressors is that their effects, even those that are experienced acutely, can have marked impacts that persist long after the initial experience. Although the majority of neurobiological changes in response to acute stressors are short-lasting, being apparent for a matter of minutes or hours, these neurochemical processes can be sensitized (primed) so that when animals are again exposed to the stressor at a later time, these changes will readily be reinstated (Anisman et al., 2003). Indeed, some of these actions can be engendered by cues that had been associated with the stressor (in human research these cues are described as "triggers"). These sensitizing actions might not be observable on a day-to-day basis but may be pronounced upon subsequent exposure to a stressor. Sensitizing actions are not necessarily limited to responses when the same stressor is encountered, as cross-sensitization can occur so that an exaggerated response is elicited when a different stressor is subsequently encountered. For example, studies in animals demonstrated an exaggerated response among previously stressed rodents upon exposure to a different stressor, and was further apparent in response to drugs that affect monoamine activity, such as amphetamine or cocaine, as well as morphine (Anisman et al., 2003; Bland et al., 2003; Uban et al., 2015). Likewise, stressful experiences can result in the sensitization of pro-inflammatory processes so that responses to later immune signaling molecules (cytokines) are exaggerated (Anisman et al., 2003). Sensitization to stressors was initially observed in relation to norepinephrine and dopamine activity, but these processes have since been documented in relation to multiple neurotransmitters, hormones, growth factors, and inflammatory processes that have been linked to psychological and physical illnesses (Anisman et al., 2018). What this means for refugees is that the experiences from which they fled might continue to impact their responses to subsequent unrelated stressors, affecting underlying biological processes, along with appraisals and coping strategies (Matheson et al., 2008).

Predictably, reminder cues associated with a traumatic stressor may instigate profound neurobiological effects in animals and in humans (Matheson and Anisman, 2012). Moreover, periodic presentation of stressor reminders over the weeks following an initial trauma may limit the dissipation of processes that would otherwise permit the organism to recover (Maier, 2001). This has obvious implications regarding vulnerability to stressor-related pathologies, but might be an important feature with respect to the building of resilience. For instance, what are the features of the stressor (or the stressor context) that allow for an adaptation to the impact of stressors under some conditions (or in some individuals), but promote sensitization of neurobiological processes in other instances? In this regard, women in abusive dating relationships were found to show marked increases in cortisol levels in response to reminder cues of abuse, whereas ethnoracial minorities exposed to reminders of traumatic discrimination did not (Matheson and Anisman, 2012). Under what conditions might previous experiences with controllable stressful events allow individuals to become immunized against the adverse effects of subsequent stressor experiences? Might having effective social support or positive nurturing early life experiences act in a similar capacity to promote resilience in the face of later stressor challenges?

It has been maintained that although severe stressors, particularly those experienced early in life (e.g., witnessing the assault or death of a parent), may have lasting negative consequences, encountering *tolerable* stressors (i.e., those that can be overcome by personal resources or with effective social supports) might engender resilience, as the individual learns the effective use of certain coping strategies, or to be flexible in their coping strategies as the situation demands (McEwen, 2020). This said, stressors that on the surface appear tolerable (e.g., racial micro-aggressions; psychological abuse) can, in fact, create persistent distress that culminates in pathology, particularly when such *apparently* mild stressors are encountered repeatedly. In this regard, the well-being of Somali refugees to Canada was more strongly associated with assimilation stressors encountered

than with their exposure to the violence in Somalia (Jorden et al., 2009).

Coping by Meaning Making

Although traumatic experiences frequently engender negative outcomes, this shouldn't be misunderstood as implying that traumatic stressors will necessarily have such repercussions. There are instances in which intense stressors enhance resilience (i.e., "what doesn't kill us might actually make us stronger"), perhaps being dependent upon when the stressor was encountered (e.g., during childhood or as an adult), and the protective resources that were at hand to contend with it (e.g., a caring and empathetic source of social support).

Severe trauma undermines fundamental beliefs about the world (Janoff-Bulman, 2010), and the ability to generate a sense of coherence and derive positive meaning from the event may be a fundamental coping strategy. Individuals who had experienced trauma, but found meaning through their hardships (benefit finding, posttraumatic growth), were less likely to succumb to psychological disorders (Davis et al., 2000; Albuquerque et al., 2017) and were better able to cope with further challenges (Hamama-Raz et al., 2019). More than 70 years ago, (Frankl, 1946) reflected that, even if we are unable to avoid suffering, we can choose how to cope with it, perhaps *finding meaning* in it, and then move forward with renewed purpose and hope.

Along these lines, collective interpretations of the violence refugees experienced contributed to their capacity to find meaning and to carry on effectively with their lives. For example, war-related violence was interpreted by Somali refugees as a political assault on tribal lineage. As a result, rather than dwelling on their personal suffering, these refugees appeared to establish social norms that guided their interpretation and response to events, and this shared understanding may have limited psychological distress (Zarowsky, 2000; Elsass, 2001).

Collective interpretations do not always promote resilience but might instead promote feelings of loss (Jorden et al., 2009). Individuals from war-torn communities that dwelled on the violence and destruction of the social structure demonstrated greater distress than those from communities that focused on notions of resistance (Abramowitz, 2005). In this regard, the collective interpretations of refugees who are in exile might comprise a sense of loss and dislocation. Re-establishing a sense of connection with other refugees might help to recreate a counter-narrative of strength and agency. Social support may play an especially poignant role in the well-being among refugees by maintaining a shared interpretation of their collective experiences, and by providing social resources to contend with acculturation stressors (Jaskinskaja-Lahti et al., 2006). Perhaps for this reason, those who became actively involved in helping other refugees were better able to make sense of their experiences, and experienced less distress associated with their losses and acculturation stressors (Puvimanasinghe et al., 2014). Such *altruism born of suffering* has been found to promote healing and growth among trauma survivors (Vollhardt, 2009). It is suggested that such altruistic behaviors allow survivors to transform the meaning of past suffering in a manner that allows for psychological growth and collective resilience (Staub and Vollhardt, 2008).

Spiritual Connections: Finding Meaning and Purpose in an Unsafe World

Traumatic events often challenge core values and beliefs about safety, self-worth and the meaning of life (Janoff-Bulman, 2010). Accordingly, in the aftermath of such experiences, espousing particular spiritual or religious world views, practices, and ceremonies is a common response to life-changing events (Peres et al., 2007), including in response to refugee trauma (Bryant-Davis and Wong, 2013; Adedoyin et al., 2016). Spirituality is sometimes viewed as a personal experience and set of practices, whereas religion reflects a commitment to a collectively agreed upon set of beliefs and doctrines recognized by a sacred institution. In both instances, however, they reflect individuals' connection to a higher entity, and in so doing provide life purpose and meaning (Starnino, 2016), perceptions of control in an unpredictable world (Kay et al., 2008), and serve as a basis for self-enhancement (Sedikides and Gebauer, 2010).

Although there is little question that the factors that contribute to resiliency in the aftermath of trauma vary cross-culturally (Ungar, 2008), turning to some form of religious belief appears to be a common source of re-assurance and meaning. It has been estimated that 84% of people globally affiliate with a religious group (Pew Research Centre, 2017). After the September 11 attack on the World Trade Towers in the United States, 90% of Americans allegedly turned to religion or spirituality to cope (Schuster et al., 2001). Religion places control of traumatic events in the realm of a higher order, allowing followers to derive a sense of coherence in the experience, that what happened was destined to be, and that there is reason to have hope for the future (Peres et al., 2007), which together bolster resilience (Masten, 2015). It is also possible for individuals to foster a sense of partnership with a divine being, working together to problem solve (Wilt et al., 2019). The stability of spiritual and religious worldviews over time and place may also satisfy the need for belongingness and offer confidence in the midst of uncertainty (Ysseldyk et al., 2010).

Religiosity also serves as an important social identity, and as a result may contribute to providing an effective source of social support. However, it is also unique in that it invokes guiding epistemological and ontological beliefs about human existence that are shared among group members (Ysseldyk et al., 2010). Historical and cultural continuity grounds these core beliefs in rites, symbols, and physical spaces created over millennia but adapted to fit with shifting social norms and ways of living in a given era (Haslam et al., 2010). Thus, religious affiliation is not simply another social identity, as its positive effects depend on the confluence of spiritual belief, social participation, and establishing a strong congregational social network (Lim and Putnam, 2010). In effect, individuals not only gain a sense of belonging, but also benefit from a set of guiding beliefs that offers a worldview entailing life purpose and meaning (Bryant-Davis and Wong, 2013).

This said, spirituality is not always an effective protective factor. It also happens that trauma can undermine beliefs in a higher power, as victims feel that "God has abandoned me" (Pargament et al., 2001; Bryant-Davis and Wong, 2013). This might be especially the case when individuals encounter a morally injurious event, which has been defined in numerous ways, but essentially involves events that damage a person's conscience or moral compass as a result of perpetrating, or failing to prevent, acts that transgress deeply held moral beliefs (Litz et al., 2009). The resultant moral injury has been referred to as a "a deep soul wound that pierces a person's identity, sense of morality, and relationship to society" (Silver, 2011). Although primarily studied among military personnel exposed to combat, such events might also affect others exposed to violence, such as refugees, journalists, front-line personnel in a natural disaster, or among hospital staff forced to weigh provision of treatment (Barnes et al., 2019). Such events can give rise to existential issues, wherein individuals question their moral worth, goodness in the world, and spiritual faith. While moral injury might co-occur with PTSD, they are mechanistically different, in that the latter is more likely to be fear-based (Barnes et al., 2019), and functional brain connectivity changes associated with moral injury and PTSD could be distinguished from one another (Sun et al., 2019). Moral injury (the potential outcome of encountering such an event) also differs from the consequences of other life-threatening traumas, being more strongly associated with post-event emotions [shame, guilt, (self-)contempt, fear of judgement], rather than those experienced during the event (Barnes et al., 2019). It has been suggested that healing moral injury might entail re-establishing interpersonal trust (through compassion and loving kindness) (Hinton et al., 2013), and resolving spiritual struggles (through forgiveness and repentance) (Pearce et al., 2018).

SCENARIO 3. INDIGENOUS PEOPLES' COLLECTIVE AND HISTORICAL TRAUMA

Indigenous Peoples in many regions of the world have been subjected to colonialist acts intended to eradicate their culture and traditions, if not the people themselves. In North America, European colonizers forcibly drove Indigenous Peoples off of their lands to the confines of reserves. As well, their children were abducted and placed in residential or boarding schools with the explicit goal of severing familial ties and cultural socializations while instilling Euro-Christian values, including an understanding of racial hierarchy. Concurrently, legislative policies were enacted that disempowered Indigenous Peoples, outlawed cultural and spiritual practices, and effectively rendered them wards of the state. As a result of historical trauma and ongoing systemic racism, current generations of Indigenous Peoples disproportionately experience high rates of suicide, substance use, depression, anxiety, diabetes, and respiratory illnesses, to name but a few (Gone et al., 2019; Menzies, 2019). At the same time, there are many strong Indigenous Peoples who are fighting to restore their cultural traditions, reclaim possession and self-determination of their lands, and overturn the racialized injustices and legislative acts of the colonizers.

It should be clear that the appraisal processes (controllability) and sensitization effects associated with early life and traumatic stressors are relevant to the experiences of Indigenous peoples, and as will be discussed, have repercussions across generations. Social relationships are core to Indigenous values and meaning-making, reflected in connections to family and community, and extending across generations from offspring to ancestors in the spiritual world (Kirmayer et al., 2012). Indeed, the holistic understanding of wellness that is fundamental to most Indigenous worldviews emphasizes the importance of relationships and the value of connection to all that is animate (Kimmerer, 2013).

Stressor Chronicity and Allostatic Overload

Inherent to the concept of historical and transgenerational trauma is exposure to pervasive, repeated, chronic stressors that affect a group as whole. Although individuals may encounter numerous acute stressful events, those that appear most damaging to psychological and physical health are chronic challenges. Chronic stressors have been tied to severe psychological disturbances (e.g., depression, anxiety, PTSD, substance use), as well as a host of inflammatory-related physical disorders, such as diabetes and heart disease (Furman et al., 2019). The development of these disorders varies with several other variables, including previous stressful experiences, such as early life adversities (e.g., neglect, abuse, illness-related hospitalization, maternal depression, parental substance use), and was more prominent in vulnerable populations (e.g., those with subclinical illness features, in older individuals, and those living in poverty or who maintained poor lifestyles). Early life challenges stemming from transgenerational trauma associated with parental attendance at Indian Residential School are further related to a proliferation of stressors in childhood and adult life (Bombay et al., 2014, 2017), and the combined effects of the accumulation of multiple stressors may operate much like stressor chronicity (Steptoe and Kivimäki, 2013). It should be said that while early life stress emanating from abuse, death of a loved one, or domestic violence were linked with later depression, other stressors, such as illness and natural disasters, and even poverty were less likely to be related in a similar manner (LeMoult et al., 2020). These latter stressors may have been more responsive to protective social factors, including familial or community solidarity, as well as spiritual connections.

As discussed earlier, stressors ordinarily elicit multiple neurotransmitter, neuroendocrine, immune, inflammatory, and peripheral nervous system changes that are presumed to have adaptive value. These neurobiological adaptations (allostasis) operate together with behavioral, cognitive, and social processes to maintain well-being. As much as this is highly adaptive, should these neurobiological processes be engaged for protracted periods, *allostatic overload* may be experienced, which could provoke negative repercussions on particular brain neural circuits and body systems (McEwen, 2000). By example, persistent release of glucocorticoids could disturb hippocampal corticoid receptors, so that an essential

shut-down mechanism for hypothalamic-pituitary-adrenal activation is impaired, resulting in sustained adrenal cortisol release, leading to further hippocampal disturbances (McEwen, 2007). Likewise, the changes of norepinephrine and serotonin utilization initially provoked by an uncontrollable stressor are elevated with a chronic stressor that might be met with a compensatory increase of synthesis. However, this presumably adaptive change can persist for only so long before maladaptive behavioral consequences are apparent (Anisman et al., 2018). The reduced hippocampal BDNF gene expression and protein levels induced by acute stressors (Duman and Monteggia, 2006) were still more pronounced following a chronic stressor regimen in rodents (Grønli et al., 2006). It appeared that the actions of a chronic stressor regimen on hippocampal BDNF were more pronounced in females than in males, which is in keeping with the greater depression vulnerability in human females (Liu et al., 2019). In addition to the differential effects of acute and chronic stressors on neurobiological processes, very different effects on immune functioning and the production of chronically elevated inflammatory processes have also been documented (Dhabhar, 2014).

Many different biological checks and counterchecks occur in an effort to maintain allostasis. For instance, the decline of monoamine levels provoked when acute uncontrollable stressors cause utilization to exceed synthesis might not be evident in response to chronic stressors. As a challenge continues, a compensatory increase of neurotransmitter synthesis may occur, meeting the high rate of utilization, so that monoamine levels may normalize. This may be highly adaptive in the short and medium term as it allows the organism to deal with ongoing challenges. It is tempting to assume that under these conditions the storm has been weathered and that things are under control. In fact, however, when increased utilization and receptor activation persist for an extended period, an excessive load is placed on critical systems. Likewise, chronic stressors may diminish innate and acquired immune functioning, and dysregulate inflammatory processes that favor the emergence or exacerbation of various illnesses if they already exist or are at subclinical levels (Anisman et al., 2018).

Allostatic overload is most apt to occur when the chronic stressor does not readily allow for adaptation (e.g., when the stressor occurs on an intermittent, uncontrollable, and unpredictable basis leading to still greater neuronal activity). In addition, individuals who experienced earlier or concurrent social and environmental insults, such as those related to work, home-life, poverty, and social factors may be especially vulnerable to the development of allostatic overload (McEwen and Akil, 2020). Given that diet, obesity, exercise, and sleep also affect many stress-relevant processes, including inflammation and microbiota that affect immunity (Cryan et al., 2019), these should also be included in the mix of factors that could affect allostasis and allostatic overload. Importantly, most stress-related illnesses do not simply appear overnight but reflect the accumulation of chronic small changes that develop with repeated insults over an extended period (Dube et al., 2003), pointing to the importance of evaluating the impact of chronic challenges in relation to disease occurrence.

These persistent effects of stressors can be detected throughout life irrespective of when the initial negative experience was encountered. Significantly, the proactive effects of stressors in relation to neurotrophins, inflammatory mechanisms, and gut microbiota were particularly prominent if they had been experienced during early life (Burns et al., 2018; Audet, 2019). Such outcomes may reflect the sensitization of neurochemical systems, or the introduction of epigenetic changes that manifested as altered responses to later challenges (Szyf, 2011; Torres-Berrío et al., 2019). Further to this, stressors over the lifetime can have cumulative actions that favor the development of pathological outcomes, more so if the actions of stressors had been "embedded" during childhood through epigenetic changes and then exacerbated by further stressor encounters (Szyf, 2019). The initial stressor experiences may provoke cascading neurobiological changes, essentially modifying the organism's developmental trajectory so that basal biological functioning was permanently altered. Regardless of the mechanism, it is certain that adverse early experiences can have long-lasting ramifications that can emerge at later times, particularly if a stressor was again experienced. Owing to the plasticity of brain networks, both positive and adverse early experiences are the seeds that are laid down to bloom at later times.

Quite literally, historical or transgenerational trauma presents challenges that occur over generations. Historical trauma refers to the suffering that results from a collective history of colonization and its implications for disrupting traditional ways of life, culture, and identity (Brave Heart and DeBruyn, 1998). This underscores the explicit connection between the trauma experienced by previous generations on the well-being of descendants, and the continued gaps not only in individual wellness outcomes (Gone et al., 2019), but the implications for ongoing collective rights, functioning, and systemic discrimination (Bombay et al., 2017). Moreover, the view has been entertained that the biological consequences of traumatic experiences can be carried across generations though epigenetic changes, so that the descendants of survivors may be more vulnerable to later stressor challenges (Szyf, 2015; Cavalli and Heard, 2019). At the same time, it is possible that epigenetic changes (and psychosocial processes) associated with historical trauma could instill individuals with greater adaptability and resilience (Lehrner and Yehuda, 2018; Yehuda et al., 2018). Such a possibility can be derived from studies in rodents indicating that prenatal stressors could promote epigenetic changes that were advantageous in the context of threatening situations (St.-Cyr and McGowan, 2015). In effect, although prenatal and early life stressors could produce disadvantageous epigenetic changes, their ultimate actions may be context dependent.

There has been impressive evidence from animal studies showing that epigenetic effects can be promoted by stressful experiences as well as by a variety of toxicants. For instance, epigenetic changes related to prenatal or early life stressful events have been observed in relation to genes coding for glucocorticoid receptors (Grundwald and Brunton, 2015; Turecki and Meaney, 2016), the serotonin transporter (Kinnally et al., 2010), estrogen receptor alpha (Champagne, 2008), inflammatory

factors stemming from infection (Weber-Stadlbauer, 2017), as well as many other biological factors relevant to physical and mental health disturbances. These epigenetic changes can occur within germline cells (sperm or egg), and thus, could be recapitulated across multiple generations (Franklin et al., 2010; Bohacek and Mansuy, 2015; Jawaid et al., 2018). These transgenerational outcomes (i.e., those that span at least three generations) may well be responsible for diseases brought about by stressors, infection, and by pesticides (Franklin et al., 2010; Manikkam et al., 2014; Weber-Stadlbauer, 2017).

The data concerning transgenerational effects in humans are sparce given the difficulties of obtaining DNA from descendants of traumatized individuals. Nonetheless, as historically traumatized groups, including Indigenous Peoples in Canada, Australia, and the United States, have experienced marked health disparities (Bombay et al., 2014), it has been suggested that this might stem, in part, from epigenetic changes (Conching and Thayer, 2019; Phillips-Beck et al., 2019). To be sure, numerous factors that emanated from historical trauma could account for these outcomes (e.g., poverty, poor maternal care of infants, limited childhood education, lack of medical service, a sub-optimal intrauterine environment, continued systemic discrimination) making it exceedingly difficult to identify the relative contributions of these numerous variables, including the role of epigenetic influences (Gone and Kirmayer, 2020). As often said, however, "the absence of evidence, does not imply evidence of absence."

A relatively small number of studies were reported concerning intergenerational epigenetic effects in humans. Among the offspring of holocaust (Shoah) survivors, the risk for PTSD (or subthreshold features) was elevated in a subset of individuals. This risk was most evident in relation to several parental and child characteristics (e.g., parental mental health problems, attachment quality, having both parents be Holocaust survivors), and having encountered their own stressors (Dashorst et al., 2019). Cortisol levels were reduced among children of Holocaust survivors, which has been observed in relation to PTSD under other circumstances. Interestingly, cortisol levels in offspring were inversely related to parental PTSD symptoms (Yehuda and Bierer, 2008). More to the point of this discussion, PTSD and depression among Holocaust survivors were associated with the increased presence of epigenetic changes within the FKBP5 gene (Yehuda et al., 2016) that has been associated with glucocorticoid functioning and systemic inflammation (Zannas et al., 2019). An epigenetic change of the FKBP5 gene was also apparent in their offspring; however, in this case epigenetic marks were reduced (Yehuda et al., 2016; Bierer et al., 2020). It is uncertain whether this epigenetic effect in offspring reflects a vulnerability factor for later pathology or an adaptive change to limit excessive cortisol output.

Like the studies conducted with the offspring of Holocaust survivors, severe prenatal stressors stemming from war-related trauma may also instigate epigenetic changes related to BDNF as well as cortisol-related processes (Monk et al., 2016). Aside from the influence of these severe stressors, maternal adversity in the form of nutrition scarcity, preeclampsia, smoking, and diabetes, were accompanied by epigenetic changes of glucocorticoid-related genes (Nagarajan et al., 2016). Not unexpectedly, among women who experienced interpersonal or community violence while pregnant, psychiatric illnesses and epigenetic changes related to glucocorticoid functioning were frequently observed in these women, their offspring, and in their grandchildren (Serpeloni et al., 2017). Curiously, however, if the offspring of women who experienced violence encountered subsequent stressors, then these psychiatric outcomes were not apparent. Among the offspring of abused women, epigenetic changes were apparent at genes that encoded the glucocorticoid receptor (NR3C1), and its repressor (FKBP5), which might allow for greater ability to limit stressor-provoked cortisol responses (Serpeloni et al., 2019). Paralleling the effects of interpersonal violence, among the children of prenatally stressed middle-eastern refugees, similar outcomes were observed upon later war-related stressor exposure (Serpeloni et al., 2019). It should be added that epigenetic actions related to glucocorticoid functioning is only one of many neurochemical, neurotrophic, and hormonal factors that have been linked to trauma experiences, and it remains to be established whether any of these are subject to transgenerational effects (Kertes et al., 2017; Simons et al., 2017).

Although research dealing with epigenetic changes, as well as with allostatic overload has often focused on the impact of chronic strain within individuals, the insidious threats that comprise sustained social disturbances, social conflict, racism, and poverty can engender *type 2* allostatic overload, reflecting systemic rather than individual stressors (McEwen and Wingfield, 2003). While this form of allostatic overload can seriously undermine well-being, its resolution is less individual and more institutional and political, requiring altered social structures to prevent the development of pathological conditions (McEwen and Akil, 2020). As much as individuals might believe that behavioral change that acts against stressors and promotes good health is related to their own self-efficacy, lasting impacts may be profoundly influenced by their social groups, community initiatives, and broad government policies.

A Place Called Home: Connection to Land

While colonization dominates the historical context of Indigenous Peoples' current wellness, strength, and resilience can be derived through a connection to the land and places that ground people in an identity, self-affirmation, belonging, and safety (Hopkins and Dixon, 2006). Among Indigenous Peoples, such connections are further imbued with spirituality, and promote a continuity of relationships across generations. In this regard, spiritual connections are not limited to moral or existential beliefs, but might also have links within the tangible world, including spaces that provide us with a sense of being "at home" with ourselves or, much like religious beliefs provide individuals with a sense of belonging in the universe. Physical places can be both natural or built spaces (such as one's home, church or workplace). Such spaces might be broadly defined (e.g., "by the ocean") or might entail very specific locations that are "grounded in local ecologies, through cultural knowledge and practices" (Gone and Kirmayer, 2020). In this regard, a

sense of place refers to how individuals characterize, experience, use, and understand places, as well as functional, subjective, and emotional attachments to these places (Graham et al., 2009; Lewicka, 2011). Most places are shared spaces and therefore also provide the foundation for social connectedness, identity, and a sense of belonging (Qazimi, 2014). A strong social community associated with a place can serve as a protective factor against the negative impacts of other environmental stressors (e.g., poor living conditions) on well-being (Fong et al., 2019). When place-based social relationships become inaccessible (e.g., due to retirement, or migration), well-being is diminished (Atkinson et al., 2016). Conversely, during place transition, maintaining place-based social ties can alleviate feelings of dislocation and thus, act as a source of resilience (Chow and Healey, 2008; Scopelliti and Tiberio, 2010).

The relative importance and meaning of a place can vary based on cultural background, residential status, and personal history (Wilson, 2003). In particular, at the heart of many Indigenous cultures, the land is infused with meaning that is expressed through language, stories, music, and art. Resilience derived from the symbiotic relationship to the land often involves the integration of cultural identity with the features of specific places. This relationship not only reflects an appreciation of the physical features of a geographical location, but also encompasses non-physical elements, such as the social, emotional, and spiritual aspects that provide the foundation of identity, and a sense of community and belonging (Wilson, 2003; Graham et al., 2009; Qazimi, 2014). In this regard, Indigenous elders reported that a strong attachment to the land maintained through ceremonial practices, community involvement, traditional food sharing, and use of traditional language were essential to affirming land-based and cultural identities, which in turn, protected them from adverse health effects and promoted physical, mental, and spiritual healing (Tobias and Richmond, 2014). Reflecting beliefs in the healing properties of connecting to the land, programs that encourage land-based activities have been emerging across Indigenous communities as a strategy for building youth resilience (Walsh et al., 2018). The objective of these programs is to build confidence, esteem, cultural connections and positive relationships among youth that may help them to contend with the challenges they encounter (Hackett et al., 2016; Walsh et al., 2018).

Predictably, disturbances to a place that are beyond an individual's control can result in feelings of *placelessness* (Wilson, 2003). Such disturbances may be especially marked during exile or forced transitions (as in the case of refugees), such as the environmental dispossession forced on many Indigenous populations (Tobias and Richmond, 2014). Such dispossession can be direct as a result of major changes to landscapes (e.g., construction of railroads, highways, dams), pollution, and limited access to the land preventing its use for ceremonies and traditional practices. However, indirect dispossession can also occur when, for example, language is lost, as Indigenous languages are often grounded in meanings that have evolved in relation to the home land. In this regard, historical colonialist actions involving involuntary relocations and restriction of movement, together with ongoing assimilationist policies associated with education, loss of language, health and governance, have all contributed to the erosion of the knowledge of the land that was passed down through generations, including a holistic understanding of social purpose and meaning (Allen et al., 2014). At the same time, many Indigenous Peoples, even those living in urban settings, report strong identification with their home communities (reserves), despite the impoverished infrastructure (water, housing, community centers, schools) emanating from systemic underfunding. Such community (or neighborhood) identification is associated with positive mental health that overrides the lack of community resources and socioeconomic disadvantage (Fong et al., 2019), affirming the importance of place identity as a resilience factor.

Although connection to the land is an integral part of most Indigenous cultures, recognition of the healing properties of spending time in nature is also emerging in more mainstream interventions to promote resilience and wellness (Pálsdóttir et al., 2018). Several reviews have concluded that immersive nature experiences are associated with positive well-being, cognitive, and social functioning, and a reduction of stress and other risk factors associated with diminished mental health (Bratman et al., 2019; Mygind et al., 2019). Moreover, connection to nature was associated with self-reported personal growth (Pritchard et al., 2020). Nature experiences can range from spending time in urban green spaces, gardening, activities or outings in natural settings, and fishing, hunting or being in the wilderness; at the same time, there is little clarity on the kinds of experiences that contribute most to well-being, how much time in nature is needed to feel a sense of connection, or for whom such contact or connection is most beneficial (Frumkin et al., 2017). Numerous key qualities might contribute to the restorative effects of nature, including the provision of sanctuary or refuge, prospect (i.e., open space with vistas), and a safe and secure space (Pálsdóttir et al., 2018). Such features may serve to reduce stress and relieve mental fatigue, increase physical activity and social connections, expose people to improved air quality, and enhance immune function (Frumkin et al., 2017). In addition, access to such spaces might provide a *third-place* (outside of home and work) that might operate as a safe haven that facilitates well-being (Fong et al., 2020), which may be especially relevant to women seeking refuge from an abusive home environment. Although some of the benefits of third-places cater to social needs (Fong et al., 2020), they might also serve as a refuge that allows the individual to disconnect from day-to-day stressors and reconnect with nature.

While connection to the land might be a source of resilience, changes to the land as a result of climate change are not only dispossessing those who inhabit and rely on it, but is serving as a traumatic stressor in itself (Cunsolo-Willox et al., 2012). When the land is the main source of sustenance, the inability to predict environmental phenomena, or the lack of tools to contend with such changes, can have particularly devastating effects on well-being at both the individual and community level. In addition, when extreme events (e.g., fires, floods, hurricanes, earthquakes) force displacement, temporarily or permanently, there is the additional diminishment of the safety and security of displaced populations. Under these conditions, resources (e.g., financial,

along with basic needs such as water, food, clean air) are stretched or no longer accessible, family, and community members may be divided or lost, safety, and security are undermined, and exposure to potential toxicants and disease are heightened. Thus, having once had a protective factor to which individuals could turn in the face of stressors, cumulative or extreme environmental changes may be distressing, particularly for those populations that were most vulnerable prior to such events (Johnson and Galea, 2011). Nonetheless, resilience in the aftermath of such challenges does occur. It has been suggested that resilience is fostered when the survivors of natural events are able to express and anticipate collective solidarity and cohesion, and to act cooperatively to draw on collective social support resources (Drury et al., 2019). The emergent properties of a "ground-up" shared identity may be fundamental to establishing the social behaviors that promote collective resilience.

DISCUSSION

The processes underlying resilience are complex, involving the dynamic and reciprocal interaction of many moving parts. We often consider the contributing factors in a causal flow, and indeed, this has allowed us to learn much about the mechanisms triggered by stressful events. However, this approach also has limitations. In this regard, we sought to depict several pathways that might be evident in relation to specific stressor contexts, and in particular considered how various underlying biopsychosocial processes and resources might contribute to longer-term resilience and well-being in the aftermath of traumatic stressors. These stressor contexts included women's recovery upon termination of an abusive intimate relationship, the adaptation of refugees who had fled violence to establish a new life in a host country, and Indigenous Peoples' reclamation of traditional sources of strength following historical and transgenerational trauma within their own nation. Our objective in doing so was to highlight the complex interplay among elements as they unfold over time and the course of the stressor. This said, although we incorporated particular processes within a given stressor context, these elements could have been equally applied to the other contexts. Specifically, each of these traumatic experiences may be subject to the sensitization of neurobiological systems; in each case, the distress is typically chronic, often with uncontrollable features leading to allostatic overload and the emergence of subsequent pathology. In addition, processes that promote the sense of safety that are fundamental to sustained resilience apply to all three contexts. In this regard, spirituality may be a key source of resilience among women in the aftermath of abusive relationships (Anderson et al., 2012), and is also a fundamental aspect of Indigenous wellness (Toombs et al., 2016). Just as connecting to a place called home is central to the wellness of Indigenous Peoples, the importance of rebuilding a safe place is clearly integral to feelings of safety and reassurance needed by women leaving an abusive relationship, and to refugees fleeing violence. Finally, social relationships, whether interpersonal, familial, or community-based contribute to the well-being of refugees (Jorden et al., 2009), as well as to Indigenous Peoples (Toombs et al., 2016). Thus, although we have contextualized elements that contribute to resilience to highlight possible pathways and turning points, these processes are relevant across many contexts, interacting with the features of each.

It might also be noted that our review primarily focused on responses to social stressors. However, there are many types of stressors that call upon similar mechanisms and elicit the same challenges in their aftermath. These might include responses to diagnoses of terminal illnesses, chronic pain, job loss or financial distress, and so on. While the nature of these stressors differs substantially from those involving social phenomena, they nonetheless elicit common stress processes, including cognitive appraisals, emotional reactions, and behavioral and biological responses. Although the response pathways to social and non-social stressors might differ, in the end, they likely rely on many of the same resources to promote resilience. For example, contending with a diagnosis of a terminal illness might instigate a range of shifting appraisal and coping methods as the individual comes to terms with the diagnosis and their own mortality (Antoni and Dhabhar, 2019). However, much like social stressors, there is little question that strong social supports, a spiritual (not necessarily religious) framework for understanding their place in the world, and finding safe emotional, if not physical spaces, that provide them with some respite, might all contribute to the psychological wellness.

This said, it is difficult to identify the specific variables that are most important in accounting for the ability to withstand diverse challenges, especially as each type of challenge may call for different resilience factors, vary across situations, and over the life span. Moreover, like the individual differences that exist in response to stressors, what constitutes resilience in one culture could be very different in a second culture, and could differ yet again in groups that have experienced cumulative, historical trauma, such as Indigenous Peoples in many countries who experienced multiple indignities over the years following colonization (Gone and Kirmayer, 2020; Matheson et al., 2021). Appreciating and understanding these cultural experiences may contribute to the development of effective interventions among at-risk populations (Ungar, 2008; Dell et al., 2011; Kirmayer et al., 2012).

Not only might various risk and protective factors act additively or interactively to contribute to resilience, but an individual may be resilient to some types of challenges and not to others (e.g., social strife vs. chronic pain may involve different processes). Some people may be more likely to develop particular stress-related outcomes, but not others (e.g., development of diabetes or heart disease, but not an autoimmune disorder). And sometimes the exertion needed to respond to one stressor might diminish the capacity to respond to others (Juster et al., 2016).

Both vulnerability and resilience might also develop through particular experiences, which may interact with genetic factors. For instance, adverse early life events are thought to have long term ramifications so risk for adult psychological (e.g., depression) and physical disturbances (e.g., heart disease) is elevated (Hodes and Epperson, 2019). The impact of these interactions varies with the age at which the adverse event

was experienced, and as a function of gender and ethnoracial group membership (Tomfohr et al., 2016; Brivio et al., 2020). Behavioral disturbances are further linked to epigenetic changes, genetic factors or the presence of particular polymorphisms. For instance, in the presence of a specific oxytocin polymorphism, stressor-related negative outcomes were less likely to develop. It had been maintained that, in addition to its apparent role in social behaviors, oxytocin may influence the salience of experiences so that under typical conditions positive early life encounters have beneficial long-term consequences, whereas negative events have adverse effects. However, individuals with particular oxytocin-related polymorphisms might not gain from positive encounters, but at the same time they might also be less affected by negative early life events (McQuaid et al., 2014).

One of the challenges of research conducted to understand stress vulnerability and resilience is that, although we might organize and conceptualize variables in a causal manner, in fact the vast majority of research is correlational, and often relies on self-report and retrospective recall. Causal understandings, and in particular those associated with epigenetic, genetic, or brain neurochemical changes are largely based on studies conducted in rodents. As much as these findings are informative, there are limits to what can be achieved through these studies. We previously described the necessary conditions for an animal model to be a valid facsimile of human disorders, as well as some of the roadblocks that can limit their usefulness (Anisman and Matheson, 2005). Aside from the difficulties of translating from animal to human conditions, particularly in view of the more complex ways in which humans appraise, interpret, and cope with stressors, the fact is that stressor-related outcomes in animals may not be fully recapitulated in humans. The ways animals contend with stressors are far more restricted than the diverse array of methods used by humans, and key social and cultural processes that promote feelings of safety are uniquely human (e.g., spirituality), although social factors and safe places may also contribute to the well-being of animals. To be sure, studies in animals allow for analyses of the interactive effects related to genetic and stressor characteristics (Prakash et al., 2006), and even permit analyses of the role of various social features (Audet et al., 2014). However, they are constrained by the validity of the models in light of the vast array of the institutional and sociopolitical factors in which human stressors are imbedded (McEwen and Wingfield, 2003; McEwen and Akil, 2020). Finally, for ethical reasons, researchers cannot subject laboratory animals to the horrid and debilitating psychological and physical stressors that humans too frequently endure (often perpetrated by other humans).

We have suggested several factors that might contribute to feelings of safety in the aftermath of a traumatic stressor that ought to contribute to resilience against negative short and long-term outcomes. However, each of these pathways to realize feelings of safety and security carry risks that need to be considered. For example, while individuals might be encouraged to seek social support, the reactions of others are not always predictable or helpful. Likewise, nurturing one's spiritual beliefs provides a world view that is comforting, but at the same time events can occur that are so injurious that they might irreparably sever the safety and reassurance found in these beliefs, even potentially exacerbating self-blame and the view that one deserves the bad things that happened. Even safe places might be violated if they were the location of traumatic experiences (such as domestic abuse, civil war, natural disasters), leaving individuals with greater loss and sense of placelessness.

To protect against the fact that the world is in actuality not a safe place, as noted at the outset of this review, it will be important to identify the constellation of factors (signatures) that might contribute to individual flexibility to garner resilience. Doing so may comprise the amalgamation of the meaning of past experiences, including both strengths and vulnerabilities, with hopes for the future; one eye looking backward, and one looking forward (Shariff, 2020). For example, among Indigenous Peoples, wellness is derived from both a strong spiritual connection to ancestors and a dedication to the futures of their children and youth. Similarly, among groups that have experienced collective trauma, learning from the perseverance of survivors is a basis for subsequent generations to recognize their individual and collective strengths. The same connections between past, present, and future are evident in many societal symbols, ceremonies, and holidays that serve as powerful reminders that foster social connections and common purpose to enhance collective and individual remembering and resilience. Thus, encouraging pathways for achieving the sense of safety that underlie resilience is a worthwhile endeavor. Pursuing such pathways may be enhanced by encouraging flexibility and a reliance on strengths in order to overcome the barriers that may be encountered along the way.

AUTHOR CONTRIBUTIONS

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The Stress of Caring—Resilience and HPA-Axis Activity in Hair Samples of Youth Residential Caregivers

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Background: Professional caregivers in youth residential care institutions experience frequent verbal and physical aggression as well as multiple stressors as part of their everyday work, leading to high levels of burnout and staff turnover. Resilience might buffer against psychophysiological stress response and therefore be crucial for well-being in professional caregivers.

Objectives: We aimed to investigate if measures related to resilience [sense of coherence (SoC), self-efficacy and self-care] and attachment security of caregivers were cross-sectionally associated with stress markers in hair samples [cortisol and dehydroepiandrosterone (DHEA)].

Method: Participants (n = 134; 64.2% women) reported on individual resilience measures and provided hair samples for cortisol and DHEA assays. Attachment was assessed in a subsample using the Adult Attachment Projective Picture System (AAP, n = 69). Linear regression models were fitted to estimate the association between resilience measures and the Cortisol:DHEA ratio, cortisol and DHEA, controlling for gender and age.

Results: SoC was associated with a lower Cortisol:DHEA ratio ($\beta = -0.36$, $p < 0.001$), driven by a positive association between SoC and DHEA levels ($\beta = 0.28$, $p = 0.002$). Self-care was also associated with lower Cortisol:DHEA ratios ($\beta = -0.24$, $p = 0.005$), due to self-care being associated with higher DHEA ($\beta = 0.21$, $p = 0.016$). HPA-axis measures were not associated with self-efficacy nor with attachment patterns in a subsample.

Conclusions: Our findings imply that youth residential care institutions might benefit from programs focusing on enhancing SoC and self-care practices. Fostering a meaningful, comprehensible and manageable professional climate in caregiving

environments and implementing self-care in routine practices might enhance not only well-being but also physical health of professional caregivers and in this way buffer adverse health effects of chronic stressors.

Keywords: attachment, HPA axis, DHEA, cortisol, self-care, self-efficacy, sense of coherence, resilience

INTRODUCTION

Professional caregivers in child welfare institutions experience multiple stressors, including frequent episodes of verbal and physical aggression and are faced with complex mental health issues of often highly traumatized clients as part of their everyday work, leading to high levels of burnout, staff turnover, and compassion fatigue (1–3). Chronic stressors are well known to alter stress responses, impair immune function and accelerate aging processes (4–6). Resilience might buffer against individual psychophysiological stress responses and could therefore be an important contributor to enhanced well-being in professional caregivers. Therefore, this paper aims to investigate if individual resilience measures [sense of coherence (SoC), self-efficacy and self-care] and attachment security of caregivers were associated with stress hormone markers in hair samples [Cortisol, dehydroepiandrosterone (DHEA), and their ratio].

Professional caregivers in youth residential care are exposed to chronic stressors and aggression resulting from their work with a highly troubled clientele. Most children and adolescents in the youth welfare system grew up in highly disrupted families, were exposed to multiple traumatic stressors or were victims of child maltreatment, and thus have an increased risk to develop mental health problems such as anxiety, depression, externalizing disorders, substance abuse, and suicidal ideation (7–19). Beyond the impact on mental health, adverse and traumatic experiences might lead to long-lasting impacts on the development of one's self-concept and identity development, inhibitory control, relationships and attachment to others, including caregivers (20–24). Therefore, it is not surprising that professional caregivers in youth welfare institutions are at increased risk to develop burnout and secondary traumatic stress symptoms or might be prone to frequent change of workplaces and compassion fatigue (3, 25, 26). Trauma exposures in juveniles may further increase the risk of hostility and physical violence against caregivers (27, 28), which in turn are related to burnout risk and psychophysiological stress responses (2). In light of the considerable stress and trauma histories of children and adolescents within child welfare systems and the high risk for chronic stress and physical and verbal aggression in their caregivers, health and well-being of professional caregivers is of essence to ensure high quality of continuous care.

Resilience is a broad and multifactorial phenomenon and concept, which comprises the ability to "bounce back" in the face of adversity and chronic stressors but also includes personal growth after adverse experiences (29, 30). With the steadily increasing attention to research on resilience in the last decades, a lively and interdisciplinary discussion about what constitutes resilience emerged (31, 32). Important resilience factors include: at least one healthy attachment figure, good caregiving and parent-child interactions, emotion regulation abilities, self-awareness and future orientation, as well as mastery, perceived social support, sense of coherence and self-efficacy (31–34). Beyond psychological perspectives on resilience, biological components of resilience include genetic, epigenetic, and psychophysiological factors (6, 35, 36). Improving and fostering resilience might thus be a promising way to enhance well-being, work-satisfaction, and health of professional caregivers to ensure a high quality of care for such a highly troubled clientele.

Concepts commonly investigated within the scope of resilience of professional caregivers in the child welfare system are sense of coherence (SoC), self-efficacy and self-care, with attachment security among caregivers becoming of increasing interest.

- The concept of SoC was established as an integral variable of the concept of salutogenesis related to the professional and healthy functioning of an individual. It contains three domains of one's perception of life as being: comprehensible, manageable and meaningful (37, 38). Antonovsky proposed SoC and general resistance resources (GRR) as two main components of salutogenesis (37). GRR can include characteristics of an individual, a group or an environment (genetic, physical, and psychosocial), which might ease effective tension management (38). Numerous studies have shown SoC to be positively related to health-behaviors and mental health and negatively toward burnout, depression, anxiety and PTSD symptoms in caregivers and medical staff (1, 26, 39–41). Others showed SoC to be an important moderator and mediator between chronic stressors, early adversity and later health outcomes (42).
- Perceived self-efficacy is conceptualized as people's core beliefs in their ability to influence events that shape their lives, which thus is the foundation of their motivation, performance accomplishments, and subsequently their emotional well-being (43, 44). A meta-analyses of 57 studies showed self-efficacy being related to lower levels of work-related burnout (45). In foster parents and child welfare staff, self-efficacy was found to be related to continued caregiving and work/caregiving satisfaction (46, 47).
- Self-caring behavior in our study, in contrast to SoC and self-efficacy, is a more pragmatic way of measuring specific health-fostering behaviors in youth residential caregivers. Self-care contains physical factors (e.g., participating in sports, sleeping enough, balancing nutrition), psychological factors (e.g., feeling supported, upholding values, self-reflection) and work-related factors (e.g., taking breaks, successfully transitioning from work to private life, sharing responsibilities). Self-care was previously shown to be related to lower levels

of burnout and lower levels of compassion fatigue (25, 26, 40, 48).
- Beyond these commonly studied constructs, attachment security was shown to be related to higher burnout and compassion fatigue levels in a review on studies in health and human service workers, as well as in dementia caregivers (49, 50).

These concepts are promising targets to enhance well-being, job satisfaction and professional functioning working in such a high stress job environment. Beyond these psychological outcomes of chronic stressors, psychophysiological measures of stress responses are of utmost interest to direct and target preventive measures toward those that also enhance physical health.

One possible way to measure the body's biological stress response is to measure hormones of the hypothalamic-pituitary-adrenal (HPA) axis, which plays a key role in responses to acute and chronic stressors. The HPA-axis is activated by the release of corticotropin-releasing hormone (CRH) in the hypothalamus, followed by the release of adrenocorticotropic hormone (ACTH) in the anterior pituitary. ACTH then initiates the synthesis and release of cortisol and dehydroepiandrosterone (DHEA) in the adrenals (51). Both cortisol and DHEA enable effective stress responses via the regulation of basal processes, such as for example immune responses and inflammatory processes (51–53). Chronically high cortisol is known to promote psychiatric illness in part through neurotoxic effects (51, 54–56), whereas DHEA is supposed to have neuroprotective effects potentially related to inhibitory effects on cortisol, due to the support of neurogenesis, and its antioxidant and anti-inflammatory effects (51, 54, 57). Measuring cortisol in saliva and blood allows assessment of acute stress responses, while obtaining cortisol and DHEA levels in hair samples allows assessment of longer-term stress responses. In particular, hair samples allow assessment of the accumulation of cortisol over time (5, 58). A commonly used measure to assess both stress hormones simultaneously is the ratio between cortisol and DHEA, which represents the balance between these two stress hormones (51, 59).

Work on chronic stress and severe early stress showed the HPA-axis to be associated with both increased or decreased stress system activity (60), with an initial hypercortisolism followed by a downregulation of the system (52). Findings on lower levels of basal DHEA in the context of chronic stress and a higher Cortisol:DHEA ratio might thus be understood as indication for a shift toward cortisol at the expense of DHEA, which would first manifest as a downregulation of DHEA, followed by a downregulation of cortisol leading to higher Cortisol:DHEA ratios (51, 61).

Despite the importance of understanding factors associated with resilience in residential youth caregivers, no study has yet investigated the association of resilience measures with cortisol and DHEA in hair samples in such a highly stressed population. Even though DHEA is a promising marker with neuroprotective potential, most studies focus on cortisol and less on DHEA mostly measuring real-time fluctuations in blood and saliva. The first studies assessing hair cortisol and DHEA to date either investigated small samples of traumatized adolescents or healthy adults (62–68). To our knowledge, this is the first study investigating the association between resilience and stress markers in hair samples in caregivers. Our study aims to investigate if individual resilience measures and attachment security of caregivers are associated with stress markers in hair samples. Specifically, we investigated the association of SoC, self-efficacy and self-care on hair cortisol, DHEA and the Cortisol:DHEA ratio. In addition, we assessed differences in hair cortisol, DHEA and the Cortisol:DHEA ratio between professional caregivers with different levels of attachment security in a subsample.

MATERIALS AND METHODS

Procedures and Sample

Surveys and well-established questionnaires were mailed to participating institutions (fourteen institutions accredited by the Swiss Ministry of Justice) at four annual sampling points. Data on sociodemographic variables, experiences of private and work-related stressors, and self-caring behavior were collected using the surveys. SoC and perceived self-efficacy were based on questionnaires. Additionally, strands of hair (3 cm) adjacent to the scalp were sampled from the posterior vertex region. Given a general growth rate of 1 cm/month, cumulative cortisol and DHEA exposures over the last 12 weeks were assumed to be indexed (55). All participants provided written informed consent. The leading Ethics Committee "Basel-Stadt" and "Basel-Land" (EKBB, Ref. Nr. 288/12), as well as the Cantonal Ethics Committee Bern (KEK-BE, Ref. Nr. 014/13), Ethics Committee St. Gallen (EKSG, Ref. Nr. 13/003), Ethics Committee Appenzell Ausserrhoden (EKAR, Ref. Nr. 34), Cantonal Ethics Committee Luzern (KEK-LU, Ref. Nr. 13009) and the Cantonal Ethics Committee Zürich (KEK-ZH, Ref. Nr. 2013-0030) approved the overall project.

A total of 164 youth residential caregivers were enrolled in the larger overall project. However, 30 of those did not provide at least one useable hair samples or data on variables for main analyses on at least one measurement timepoint during the study. In a previous analysis using cortisol data, we showed that 80% of missing data were due to participants either refusing to provide hair samples or mostly due to hair being too short to provide samples (3 cm), therefore two third of missings were men and slightly older as those participating. Included participants however did not differ on other psychosocial variables (2). Thus, 134 caregivers (48 men, 86 women) were included in the current study that provided at least one hair-sample during the course of the study (descriptives are reported in the Result section). Additionally, a subset of 69 participants additionally took part in a projective method to assess attachment style during the course of the study. These data were then used to conduct cross-sectional analyses.

Measures

Psychosocial Measures

Sense of coherence

The SoC in regard to daily work was assessed with a well-established German short version of the "Sense of Coherence Scale" by Antonovsky (7-point Likert scale with 9 items, scored 1 to 7) (69, 70). The mean was reported in the analyses. The authors of the German version reported Cronbach's alpha of 0.87 (70).

Self-efficacy

The perceived self-efficacy of caregivers was assessed with a well-established questionnaire developed for teacher populations and slightly adapted by the authors for professional caregivers (4-point Likert scale with 10 items, scored 1 to 4, from 1 = "not true," 2 = "hardly true," 3 = "rather true," 4 = "exactly true") (71). The mean score of all items is reported in the analyses. The authors reported Cronbach's alphas between 0.71 and 0.92 (71, 72).

Self-care

This self-developed questionnaire assessed physical, psychological and work-related self-caring behavior (73). The reference period reflected the past 3 months (4-point Likert scale, 24 items, scored from 1 to 4, 1 = "not accurate," 2 = "rather not accurate," 3 = "rather accurate," 4 = "entirely accurate"). After conducting a principal components analysis to reduce data, three factors were extracted and rotated using promax-rotation (kappa = 4): (a) physical factors (e.g., participating in sports, sleeping enough, balancing nutrition), (b) psychological factors (e.g., feeling supported, upholding values, self-reflection) and (c) work-related factors (e.g., taking breaks, successfully transitioning from work to private life, sharing responsibilities). In our sample, Cronbach's alpha was 0.84. The selectivity of the items ranged from 0.22 to 0.59, while item difficulty ranged from 0.56 to 0.93. The total score mean was calculated for further analyses.

Adult attachment projective picture system (AAP)

The AAP is a widely used free response measure to assess adults' attachment representation. By using a set of standardized questions, individuals are asked to tell a story in response to one neutral and seven attachment-related picture stimuli depicting scenes of solitude, death, separation and fear designed to activate the attachment system in different settings (74–77). In the present study AAP stories of the participants were recorded, transcribed, and coded by a certified judge. Story coding reflects evaluation of story content (agency of self, connectedness, and synchrony), defensive processes (deactivation, cognitive disconnection and segregated systems) and the inclusion of personal experience (76). Attachment research works with a concept of a continuum from attachment security to attachment insecurity. In a recent study a rhombus structure for the AAP was suggested operationalized as an attachment security scale by considering the classification "secure" to be on the highest position, the classification disorganized classification U ("unresolved trauma") on the lowest position and the two remaining organized insecure classifications "dismissing" and "preoccupied" on positions between secure and unresolved (78). In this present study we used this structure for measuring different levels of attachment security.

Hair Cortisol and DHEA

Hair was collected from the posterior vertex region of the scalp. Due to variability on lengths of strands of hair only strands of hair (1.5 cm long) adjacent to the scalp were analyzed. Hair cortisol and DHEA were extracted in line with the protocol by Gao et al. (79). Cortisol levels were determined using a commercially available high-sensitivity (analytical sensitivity 0.007 μg/dL) cortisol enzyme immunoassay kit (Salimetrics Europe, UK) and DHEA levels using a Salivary DHEA ELISA kit (Salimetrics Europe, UK) according to the manufacturer's protocols. Evaporated samples were resuspended in assay diluent provided by the manufacturer. The intra-assay and inter-assay coefficients of variation of these assays are below 9%. Samples were analyzed in duplicate, and mean values of respective concentrations were calculated in pg/mg hair and used in statistical analyses. All measures were performed in blinded fashion.

Analytic Plan

Before data analyses, all variables were analyzed to assess their distribution and to handle outliers. Because the distributions of cortisol, DHEA and the Cortisol:DHEA ratio were skewed these variables were log-transformed with the common logarithm (log10), which has been recommended for hormone ratios (80). After log-transformation, data were normally distributed. Univariate outliers were defined as values below the 2.5% and over the 97.5% percentile. These values were capped onto the 2.5 and 97.5% percentile for the log-transformed Cortisol, DHEA, and the Cortisol:DHEA ratio, as well as for the SoC, self-efficacy and self-care scales. These last three scales were then z-transformed to standardize these measures. Multivariate outliers were assessed for each regression model separately by calculating the Cook's Distance and excluding cases with values larger than 5 times the mean from each of the models (displayed in **Figure 1**), leading to slightly different sample sizes for regression models (n = 130–134, indicated for each of the models, see **Supplementary Tables**).

All analyses in this study are cross-sectional in nature. Analyzing the data, we first assessed the association between sociodemographic variables and the Cortisol:DHEA ratio, cortisol and DHEA using univariate analyses of variance (ANOVA) and Spearman's correlations (see **Table 1**). Second, we assessed the correlation between the Cortisol:DHEA ratio, cortisol and DHEA using Pearson's correlations (see **Table 2**). Third, we fitted linear regression models to assess the association between resilience measures (SoC, self-efficacy and self-care) and stress measures (Cortisol:DHEA, cortisol and DHEA) including age and gender in each of these models. Results are reported in **Figure 1** (plot A1–C3, additional data of these models are reported in the **Supplementary Materials**). We then conducted gender sensitivity analyses by including a gender x resilience interaction term in our models. Results are reported in **Supplementary Figure 1** (plot A1–C3 and additional data of

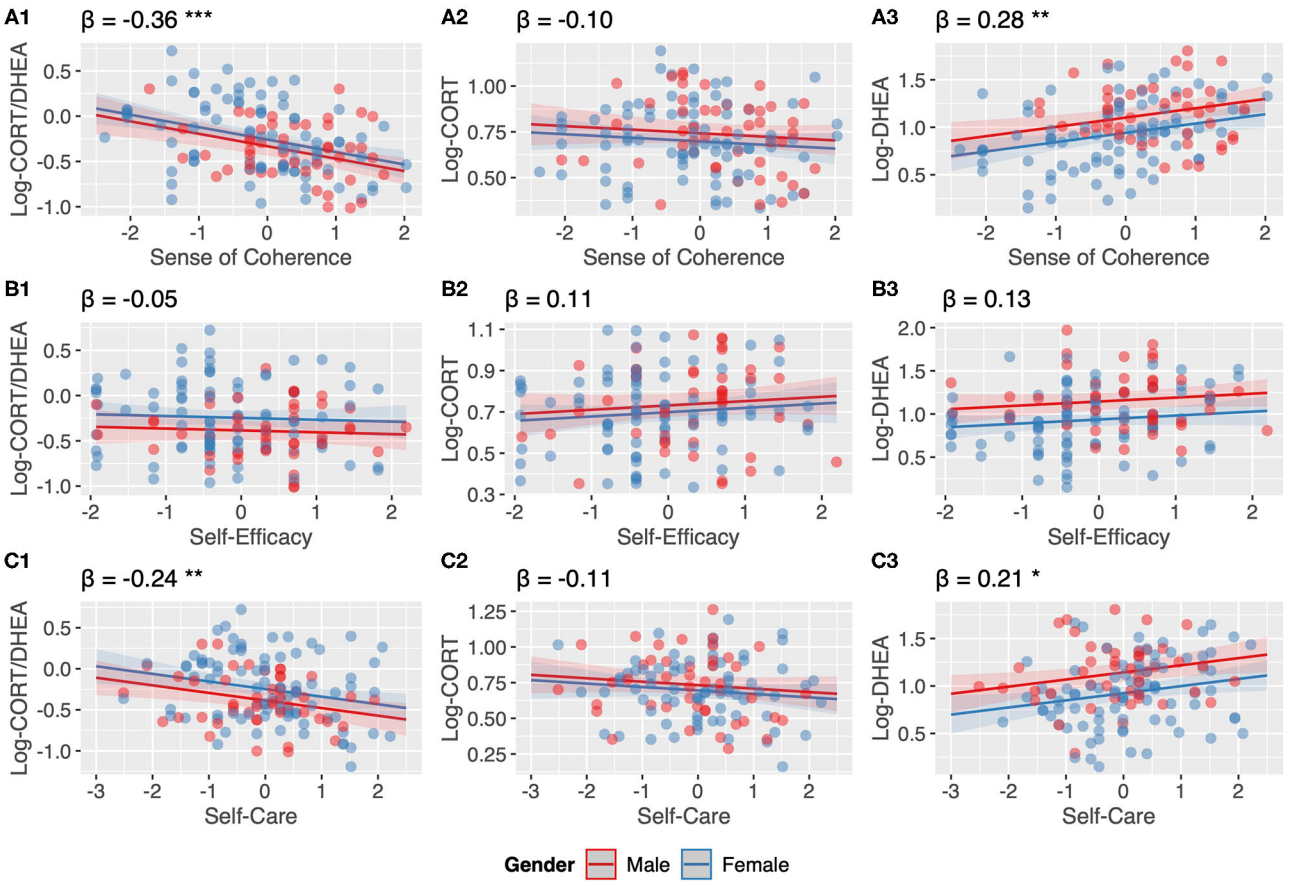

FIGURE 1 | (A1–C3) Associations between stress measures in hair samples and resilience measures from linear regression models including age and gender as covariates. β = standardized regression coefficients, * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$.

model A3 are reported in the **Supplementary Materials**). Last, we assessed differences in stress measures in hair samples of professional caregivers with different attachment representations in a subsample using ANOVA including age and gender in these models (see **Figure 2**). The statistical software used was R through RStudio (Version 3.5.2, 2018), Boston, MA, USA (81). Plots were created using the R-packages: "sjPlot" package (82) and "ggplot2" package (83). *P*-values for all models are indicated at the levels $p < 0.05$, $p < 0.01$, $p < 0.001$.

RESULTS

Descriptives

In total, 134 professional caregivers were included in the subsequent analyses. Of all participants 35.8% were men, 64.2% were women. Participants had a mean age of 35.20 years (SD = 9.54, range = 22–61) and were recruited from 14 residential youth welfare institutions. On average, they had 7.7 years (range = 0–37) of working experience in residential youth welfare institutions and had worked in the respective institution for a mean of 2.85 years (range = 0–18). Analyses of the association between sociodemographic variables with Cortisol:DHEA ratio, cortisol, and DHEA revealed gender-differences with women showing significantly higher Cortisol:DHEA ratio scores, due to significantly lower DHEA values in women compared to men (see **Table 1**).

All other associations between sociodemographic variables and stress measures and hair samples did not reach significant levels (see **Table 1**). Cortisol and DHEA levels were significantly, low to moderately correlated to each other, as were cortisol and DHEA values to the Cortisol:DHEA ratio (see **Table 2**).

Associations Between Resilience and Stress Measures

SoC was found to be negatively associated ($\beta = -0.36$) with the Cortisol:DHEA ratio, mainly due to a positive association between SoC and DHEA ($\beta = 0.28$) (see **Figures 1A1,A3**). Self-efficacy was not found to be associated with the Cortisol:DHEA ratio, nor with Cortisol and DHEA (see **Figures 1B1,B3**). Self-care was negatively associated with the Cortisol:DHEA ratio ($\beta = -0.24$), largely to due to its positive association with DHEA ($\beta = 0.21$) (see **Figure 1C1,C3**). More detailed information on these regression models (R^2, CIs, and exact *p*-values) are provided within **Supplementary Material**.

TABLE 1 | Analysis of sociodemographic variables and stress measures from hair samples.

	Log-Cort/DHEA		Log-Cort		Log-DHEA	
	M (SD)	***p***	**M (SD)**	***p***	**M (SD)**	***p***
Gender[a]						
Male (*N* = 48)	−0.40 (0.35)	**0.033***	0.75 (0.21)	0.156	1.14 (0.35)	**0.002****
Female (*N* = 86)	−0.25 (0.41)		0.69 (0.21)		0.94 (0.36)	
Stable relationship[a]						
Yes (*N* = 97)	0.29 (0.40)	0.989	0.72 (0.20)	0.832	1.01 (0.37)	0.965
No (*N* =27)	−0.29 (0.41)		0.73 (0.25)		1.00 (0.39)	
Own children[a]						
No (*N* = 85)	−0.26 (0.40)	0.061	0.72 (0.20)	0.375	0.97 (0.37)	0.106
Yes (*N* = 49)	−0.39 (0.37)		0.69 (0.23)		1.08 (0.339)	
	r	*p*	r	*p*	r	*p*
Age[b]	−0.1	0.246	−0.1	0.229	0.08	0.331
Current empl. (yrs.)[b]	0.01	0.905	0.04	0.616	0.02	0.836
Work exp. (yrs.)[b]	0.03	0.736	0.01	0.868	−0.01	0.894
Work stressors [b]	0.12	0.151	0.12	0.177	−0.05	0.555
Personal stressors[b]	−0.11	0.191	−0.02	0.855	0.09	0.28

M, mean; SD, standard deviation; r, correlation coefficient.
[a] *ANOVA.*
[b] *Spearman's correlations.*
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$.

TABLE 2 | Pearson's correlations between Log-Cort/DHEA, Log-Cort and Log-DHEA.

	Log-Cort		Log-DHEA	
	r	***p***	***r***	***p***
Log-Cort/DHEA	0.37	<0.001***	−0.84	<0.001***
Log-Cort	–		0.19	0.032*

r, correlation coefficient.
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$.

Gender-Sensitivity Analyses

All models shown in **Figure 1** were rerun including a gender x resilience interaction term. We found a gender-interactions in only one of these models, namely in regard to SoC and Log-DHEA (model A3). The positive association between SoC and DHEA is only found for women and not for men ($\beta\text{-}interaction = 0.18$). Plots regarding all of these models and a table regarding model A3 are to be found within the **Supplementary Material**.

Association of Attachment Security and Stress Measures

A subsample of 69 caregivers provided additional data on attachment security. Overall, 21.7% ($N = 15$) of caregivers were classified as secure, 69.6% ($N = 48$) as insecure (dismissing and preoccupied) and 8.7% ($N = 6$) as unresolved. We found no group differences among attachment representation groups in Cortisol:DHEA ratios, nor in levels of cortisol and DHEA (see **Figure 2**).

DISCUSSION

In this cross-sectional study on HPA axis measures in hair samples of 134 youth residential caregivers, we found resilience factors (SoC and self-care) to be negatively associated with participants' Cortisol:DHEA ratio, due to their positive association with DHEA. Secondary analyses in a subsample of participants showed no group differences in psychophysiological stress measures between groups of caregivers with different attachment styles. These findings add to only a few studies investigating the associations of resilience with cortisol and DHEA and is the first to use hair samples, a rather new approach to measure chronic HPA-activation.

Our main finding was that resilience is negatively associated with the Cortisol:DHEA ratio in hair samples due to positive associations with DHEA. In addition, we found that the association between SoC and DHEA was moderated by gender, the positive association between SoC and DHEA are only found in women. This is in line with findings of a study in 32 non-clinical adults that indicated resilience to be related to lower Cortisol:DHEA ratio in hair samples, due to a significant positive association with DHEA-S (64), a sulfate of DHEA, which in its function is closely related to its predecessor (54). In a study of female adolescents in the West Bank, sense of family coherence was shown to be moderately negatively associated with the hair Cortisol:DHEA ratio in traumatized participants only

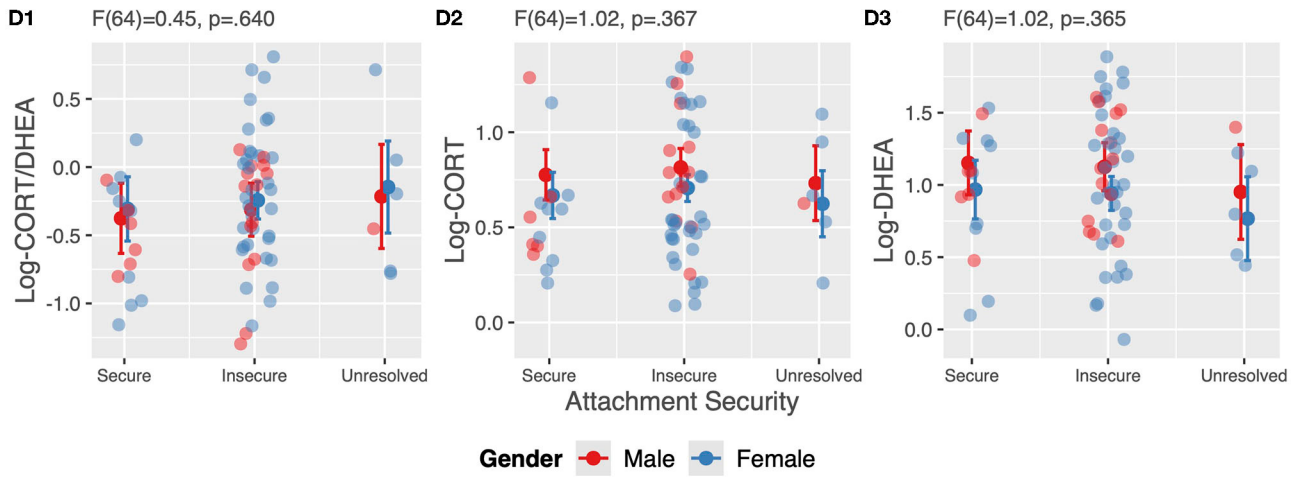

FIGURE 2 | ANOVA assessing differences in stress levels in hair samples between professional caregivers with different attachment representations including age and gender as covariates.

and positively associated with hair DHEA only in participants with PTSD (65). However, another study found no association between SoC and any of the biomarkers (65). A pilot-study of 40 healthy participants investigating hair samples found no significant associations between SoC and a resilience scale with DHEA nor with cortisol (66). In line with this study, we did not find significant associations of any of our resilience measures with cortisol in independent models including one resilience factor at a time (see **Figure 1**). Two other studies, however, found negative associations between resilience and cortisol (84, 85). Taken together, to date only a small amount of studies with small samples of limited age ranges, different assessment methods of cortisol and DHEA, and often female only either traumatized adolescents or healthy adults were published in regard to resilience and DHEA or Cortisol:DHEA ratios. Our findings add to this heterogenous body of research and provide first evidence of resilience factors being negatively associated with the Cortisol:DHEA ratio in a sample of chronically stressed adults working as youth residential caregivers.

In secondary analyses, we did not find differences in psychophysiological stress measures based on different levels of attachment security of caregivers. To our knowledge, this is the first study that assessed differences in hair cortisol, DHEA and their ratio due to different attachment representations. Our findings might be influenced by the fact, that we only had 69 participants and groups sizes with respect to attachment were not balanced (Ns = 15, 48, 6), therefore our models might be underpowered. We used the AAP, an interview using a set of ambiguous attachment related pictures representing scenes of solitude, death, separation and fear by asking the participants to tell stories to these pictures. Since youth residential caregivers are highly exposed to many extreme and horrifying stories of abuse and deprivation of their clients, these experiences from the professional context might have been projected into these attachment pictures leading to a higher degree of attachment insecurity than expected. In our sample the distribution of attachment representations was more comparable to clinical rather than healthy samples (86). This might be one explanation why no differences with respect to psychophysiological levels were found. In contrast to our results, a study in 40 healthy college students, found subjective experiences of attachment-based overprotective parental rearing to be associated with higher DHEA and lower Cortisol:DHEA ratios (87). Taken together, our results should be considered as preliminary findings on attachment security in caregivers and their association with psychosocial stress measures in hair samples. In a recent study, we found attachment-related adverse childhood experiences, in particular maternal mental illness and frequent change of caregivers to be associated with higher Cortisol:DHEA ratios in a sample of children, adolescents and young adults living in residential youth care (88). Attachment security might be an important moderator between stressors and health outcomes, as was shown between childhood adversity and cellular aging (89). Considering attachment security in future research might account for some of the heterogeneity found in the association between (early) stressors and cellular aging across studies (4, 90). Thus, more research in particular on attachment security in high stress environments and high-risk samples is warranted.

Limitations

Despite our reasonably large sample of youth residential caregivers and multiple measures of resilience analyzed in primary analyses, our findings need to be seen in light of some important limitations. First, our analyses are cross-sectional and therefore causality cannot be implied, and findings should be interpreted in light of this limitation. Second, reports on resilience measures were solely based on self-reports and recall and other biases might be apparent. Third, we were only able to measure cortisol and DHEA in the first 1.5 cm of hair and therefore only the last 6 weeks of cortisol and DHEA secretion (5), other studies, however, were able to assay 3 cm. Assessing only 1.5 cm however enabled us to include more men, whereas

other studies only investigate women for this reason. Fourth, our secondary analyses of differences in psychophysiological stress measures between groups of different attachment style are to be considered only preliminary in nature due to the rather small sample size especially when comparing groups. Moreover, we realized that assessing the AAP with caregivers in this professional trauma context has to be taken in caution and special training for administration has to be ensured in order to minimize confounds and in consequence an oblique distribution. Fifth, as we had no information on other confounding factors such as diabetes, alcohol, body-mass-index, or high blood pressure that were found to influence hair cortisol (5), we were only able to control for gender and age. Sixth, we were not able to control for different work conditions within specific institutions, due to the small sample size on the institution level. Last, resilience as a broad and multifactorial phenomenon with to date no gold-standard of measurement is hard to grasp properly from a theoretical perspective, which is beyond the scope of this paper. Therefore, we used three concepts (SoC, self-efficacy, and self-care) as proxies for overall resilience. SoC and self-efficacy are well and broadly studied concept, whereas for self-care to date there is no clear and homogenous construct defined in the literature and it is very heterogeneously assessed. These concepts were found to be moderately correlated with one another (40), which complicates individual interpretations if combined in the same model, therefore we decided to analyze them separately.

Implications

In light of our findings, promoting and enhancing resilience in caregivers might counteract the well-known adverse psychophysiological alterations associated with chronic stress (4, 5, 51). These cross-sectional correlational findings might be a first indicator of this possible health promoting effect and should be further investigated in larger longitudinal interventional studies. In a recent longitudinal study, we were able to demonstrate that SoC and self-caring behavior in youth residential caregivers protect against burnout (40). The current findings extend the protective role of resilience onto psychophysiological alterations in hair samples of caregivers. Our findings have implications for promoting self-care behavior, as well as of implementing and cultivating a meaningful, comprehensible, and manageable professional climate in all facets of caregiving environments and in particular in the broader child welfare context. The least resilient, e.g., those individuals with low SoC were shown to be the most likely to increase their SoC level in an interventional study (38). Therefore, professional trainings of health promotion practices should focus on fostering resilience capacities in such individuals (91). Several different intervention programs exist to enhance resilience and were for example shown to be able to increase sense of coherence and quality of life (30, 92). Trauma-informed self-care, which includes seeking supervision, working within teams, balancing caseloads and developing a plan for work-life balance, was found to be protective against the development of burnout and secondary traumatic stress (25). Nevertheless, two recent systematic reviews concluded that self-care still takes a back seat in social work, and little is known about the efficacy of specific self-care practices (93, 94). Trauma-informed care (TIC) concepts that also focus on implementing resilience practices for caregivers might be a promising approach for reducing the emotional burden of employees and institutions and were shown to reduce hair cortisol levels of caregivers that were trained in TIC (95). However, more intervention research implementing psychophysiological assessments of stress that replicate our findings in prospective, longitudinal studies and the integration of such findings into educational programs is needed for improving resilience and maintaining empowered and healthy caregivers.

Conclusion

This study is the first comprehensive investigation of multiple constructs related to resilience and their association to hair cortisol and DHEA levels in a sample of youth residential caregivers, a population prone to chronic stress. Sampling hair to measure cortisol and DHEA is a feasible, non-invasive approach to assess chronic stress, not only through questionnaires psychologically, but on a psychophysiological level. Our findings imply that youth residential care institutions might benefit from programs focusing on enhancing SoC and self-care practices. Cultivating a meaningful, comprehensible and manageable professional climate in caregiving environments and implementing self-care in routine practices might enhance not only well-being but also might improve physical health of professional caregivers and in this way buffer adverse health effects of chronic stressors.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because Data is only available upon request to the senior author and if shared will be protected by a signed agreement between the respective institutions that ensure ethical standards and legal requirements to be met. Requests to access the datasets should be directed to marc.schmid@upk.ch.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The leading Ethics Committee Basel-Stadt and Basel-Land (EKBB, Ref. Nr. 288/12), as well as the Cantonal Ethics Committee Bern (KEK-BE, Ref. Nr. 014/13), Ethics Committee St. Gallen (EKSG, Ref. Nr. 13/003), Ethics Committee Appenzell Ausserrhoden (EKAR, Ref. Nr. 34), Cantonal Ethics Committee Luzern (KEK-LU, Ref. Nr. 13009) and the Cantonal Ethics Committee Zürich (KEK-ZH, Ref. Nr. 2013-0030) approved the overall project. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DB, NK, CB, and MSchm were major contributors in writing the manuscript and responsible for the interpretation of the findings. DB and NK performed all statistical analyses and wrote main parts of the manuscript. MSchm and JF organized funding for the study. MSchm was PI on the study and was a major contributor to the conceptualization of the manuscript. AE analyzed hair

samples in her lab. AB was responsible for transcription and analyses of AAP interviews. NK, MSchr, VC, JF, AO'D, CB, and MSchm contributed to the interpretation and implications of the findings. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.556486/full#supplementary-material

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REVIEW
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The Contribution of Physical Exercise to Brain Resilience

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Increasing attention has been given to understanding resilience to brain diseases, often described as brain or cognitive reserve. Among the protective factors for the development of resilience, physical activity/exercise has been considered to play an important role. Exercise is known to induce many positive effects on the brain. As such, exercise represents an important tool to influence neurodevelopment and shape the adult brain to react to life's challenges. Among many beneficial effects, exercise intervention has been associated with cognitive improvement and stress resilience in humans and animal models. Thus, a growing number of studies have demonstrated that exercise not only recovers or minimizes cognitive deficits by inducing better neuroplasticity and cognitive reserve but also counteracts brain pathology. This is evidenced before disease onset or after it has been established. In this review, we aimed to present encouraging data from current clinical and pre-clinical neuroscience research and discuss the possible biological mechanisms underlying the beneficial effects of physical exercise on resilience. We consider the implication of physical exercise for resilience from brain development to aging and for some neurological diseases. Overall, the literature indicates that brain/cognitive reserve built up by regular exercise in several stages of life, prepares the brain to be more resilient to cognitive impairment and consequently to brain pathology.

Keywords: brain reserve, cognitive reserve, physical activity, exercise, neurological disorders, neuroprotection, stress, brain resilience

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INTRODUCTION

Stressful life events can have a considerable impact on brain function and structure, resulting in the development of several psychiatric disorders (Ludwig et al., 2018; Chow and Choi, 2019). Interestingly, most individuals do not develop such illnesses after experiencing stressful life events and are thus thought to be resilient. Resilience is defined as the capacity to adapt successfully to acute stress, trauma, or chronic adversity (Russo et al., 2012). In this context, researchers have introduced the concept of brain resilience, often described as brain reserve or cognitive reserve (Medaglia et al., 2017). Brain reserve is related to the structural properties of the brain (brain volume, the number and size of neurons, cortical thickness) and cognitive reserve refers to a process where the brain copes with brain pathology. Reserve of either type expresses alteration in the function or structure of the brain that modifies cognitive and behavioral capacities following brain damage (for review, see Medaglia et al., 2017). Some key brain structures involved in specific generation and regulation of emotional, cognitive, and behavioral responses to stressors include insula, nucleus accumbens, amygdala, hypothalamus, hippocampus, medial prefrontal, and

anterior cingulate cortex (Gupta et al., 2017) and dysregulation in these circuits has been related to emotional distress, anxiety, and mood disorders (Gupta et al., 2017; Iadipaolo et al., 2018).

Changes in these neural circuits affect numerous neurotransmitter systems and molecular pathways. Among them, hormones, neuropeptides, neurotransmitters systems, and neurotrophic factors are involved in the responses to stress. Alterations in their functions determine the individual variability in stress resilience (Feder et al., 2009; Russo et al., 2012). For instance, early life stress has been linked to long-lasting changes in the hypothalamus-pituitary-adrenal axis, resulting in chronically high levels of corticotrophin releasing hormone and cortisol. These events usually lead to structural changes in brain regions such hippocampus and amygdala (McEwen and Milner, 2007). Stress also induces the release of noradrenaline and serotonin in several brain areas associated to anxiety disorders and mood regulation, and dopamine in response to aversive or rewarding stimuli. Thus, considering the involvement of neurotrophins in the regulation of different forms of normal and pathological behavior, they play a critical role in resilience to chronic stress (Taliaz et al., 2011; Rothman and Mattson, 2013). Positive adaptive changes in these systems are suggested to promote resilience (Feder et al., 2009). In this regard, adaptive coping strategies in stressful situations, such as neurofeedback training have been used to reduce depressive symptoms and improve emotion regulation (Keynan et al., 2019) and a relationship between functional network at rest and resilience has been evidenced (Paban et al., 2019).

Studies have used resilience measurement scales to be applied in general and clinical populations and the Connor–Davidson Resilience Scale (CD-RISC) presents suitable psychometric properties and allows for valuable measurement of resilience (Campbell-Sills and Stein, 2007; Smith et al., 2008; Windle et al., 2011). Adapted version of brief resilience scale has been large used to this purpose.

Brain resilience or vulnerability following a stressor is influenced by innate difference (genetically determined) and the experiences or exposures of an individual across the life span (education, occupation, engagement in physical/sport activities, or social activities) (Stern et al., 2018). Therefore, the interplay between genetic predisposition and lifestyle factors has a critical role in determining resilience to brain disorders (Walhovd et al., 2019). Genetic variation, resulting alterations in neurotransmitter systems have been of particular interest for brain resilience. Differences between individuals possible reflect the interaction between genetic predisposition, early-life experiences and experiences across the lifespan. Accordingly, environmental stimuli during the early life period can exert prominent effects on the risk of neurological disorders (Lesuis et al., 2018). In this regard, a considerable number of scientific publications have reported that the combination of both physical and cognitive stimulation can affect brain resilience (Deuster and Silverman, 2013; Bozzali et al., 2015; Pedrinolla et al., 2017; Casaletto et al., 2020). The literature has clearly demonstrated that an active lifestyle is inversely associated with stress-related health problems resulting in the development of chronic diseases (Deuster and Silverman, 2013; Clark et al., 2019). Thus, healthy behaviors obtained early in life and maintained throughout a long period of life can build brain resilience against age-related diseases (Gale et al., 2012; McEwen, 2016; Lesuis et al., 2018).

Several key positive factors that occur from childhood or adolescence through to adulthood contribute to brain resilience (Burt and Paysnick, 2012). Among them, physical activity/exercise has an important role. Indeed, in many publications on resilience, one frequently mentioned factor for promoting resilience is physical exercise/fitness (Wu et al., 2013; McEwen, 2016). The beneficial influence of physical activity/exercise on resilience can in part be attributed to the understanding that it can induce positive physiological and psychological improvements, protect against the effects of stressful events, and prevent or minimize several neurological diseases. In this sense, this review will consider the following question with the target population being all life stages, including some neurological disorders, using physical exercise as intervention and brain resilience as outcome: How can physical exercise contribute to brain resilience in all life stages and in some neurological disorders? Here, we outline data generated from clinical and pre-clinical studies and discuss the possible biological mechanisms underlying the positive impact of physical exercise on brain resilience in the following conditions: (1) exercise during the pre-natal period and its effect on offspring's brain (infancy and adolescence), (2) exercise during post-natal brain development (infancy and adolescence), and (3) exercise in brain adulthood, aging, and in some neurological diseases (**Figure 1**). We focused on the impact of exercise on psychosocial stressors with regard to educational (cognitive performance), professional, and physiological performance.

Search Strategy

The literature search was conducted between February and August 2020. A comprehensive PubMed search was conducted to identify studies investigating the role of exercise in brain resilience. The following terminology was applied: ("exercise" OR "physical activity" OR "sport") AND ("stress" OR "resilience" OR "brain resilience" OR "cognitive reserve" OR "brain reserve" OR "neural reserve") AND ("neurobiological factors" OR "endocrine system" OR "genes" OR "genetic" OR "epigenetic") AND ("psychiatric disorders" OR "depression" OR "anxiety" OR "brain diseases"). Written in English, original studies, letters as well as reviews were included. Studies identified were selected and excluded by examining the titles, abstract, or full text articles. Studies that did not address physical activity/exercise for brain resilience in either clinical or pre-clinical studies were excluded.

The terms physical activity, exercise, and physical fitness are often used in the literature, and for clarification it is important to differentiate these denominations. For instance, physical activity has been used interchangeably with the term exercise." The frequently cited article by Caspersen et al. (1985) defines physical activity as any bodily movement produced by skeletal muscles which results in energy expenditure, while exercise is a physical activity that is planned, structured, repetitive, and purposeful. In contrast with physical activity, physical fitness is characterized

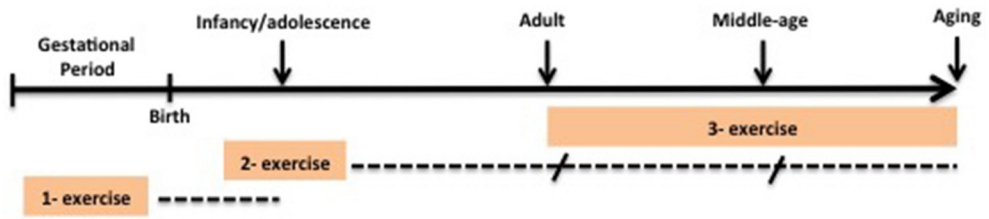

FIGURE 1 | Design of intervention studies on brain resilience in this review. Dotted lines represent follow up outcomes. (1). Exercise during pre-natal period and its effect on brain offspring (infancy and adolescence). (2) Exercise during post-natal brain development (infancy and adolescence) and its effect in later life. (3) Exercise in adulthood, aging and in some-neurologic disease.

by a number of components that an individual achieves related to health, particularly cardiorespiratory endurance, body composition, muscular strength, and flexibility. Being physically active is not necessarily the same as having high aerobic fitness.

RESULTS

Of the 147 potentially relevant articles from the PubMed database, 12 studies addressed physical exercise for brain resilience. Most were excluded because they did not address physical activity/exercise ($n = 92$) or the brain resilience outcome ($n = 43$). To conduct a scoping review looking at all life stages and some neurological conditions, both clinical and pre-clinical research, we included 114 more studies through a free search on pregnancy ($n = 9$), childhood and adolescence ($n = 18$), adulthood and aging ($n = 16$), Alzheimer's disease ($n = 17$), Parkinson's disease ($n = 14$), Epilepsy ($n = 20$), Stroke ($n = 16$), systematic reviews ($n = 3$), and clinical guidelines ($n = 1$).

DISCUSSION

For didactic reasons, we will present the translational contribution of physical exercise to brain resilience and in neurobiological conditions in the following order: physical exercise in pregnancy, in childhood and adolescence, in adulthood, aging, and neurological disorders.

Physical Exercise in Pregnancy

Brain development consists of a complex interaction of molecular, cellular, and environmental systems. It begins in the third gestational week and continues at least through late adolescence. The developing brain is constantly influenced by internal and external factors and certain events occurring during this period may positively or negatively affect the brain's development (Andersen, 2003). With respect to this scenario, evidence has shown that environmental stimuli such as physical activity/exercise can impact positively on brain development (Clapp, 1996; Esteban-Cornejo et al., 2015). Investigations on the influence of exercise at earlier stages of brain development have been encouraging, including exercise interventions on pre- and post-natal brain development.

In humans, a limited number of studies has examined whether exercise during the maternal period can influence offspring. A classic study conducted over 25 years ago demonstrated a better performance on tests of general intelligence and oral language skills in children aged 5 years from mothers who exercised during pregnancy (Clapp, 1996). In another investigation, physical activity before and during gestation positively influenced offspring's academic performance in youth (from 6 to 18 years) (Esteban-Cornejo et al., 2015). These outcomes suggest that routine exercise before and during the pre-natal period may produce benefits for infants' and adolescents' academic performance. However, whether pre-natal exercise contributes to brain resilience at later stages of life has not been explored in humans. Animal studies have provided promising data and are highlighted elsewhere in this review.

In contrast with restricted investigations in humans, a substantial number of animal studies has examined the influence of exercise during the maternal period on offspring. Evidence from laboratory animals has shown that regular physical exercise during pregnancy can affect several aspects of cognition and behavior in offspring. These findings result from experiments using different models of physical exercise, including forced treadmill running, forced swimming, and voluntary wheel running. For instance, the swimming or treadmill running exercise during pregnancy improves spatial learning (Parnpiansil et al., 2003) and short-term memory in offspring (Lee et al., 2006; Kim et al., 2007) and voluntary activity reduces depression-like behavior and increased learning and memory performance in offspring (Bick-Sander et al., 2006). The influence of exercise during the gestational period is not restricted to the offspring's cognitive functions. For instance, an acceleration of visual system plasticity was detected through earlier eye opening and visual acuity in pups from dams who lived in an enriched environment seven days before delivery (Cancedda et al., 2004). These findings indicate that pre-natal sensory-motor stimulation induces accelerated brain maturation in early post-natal life.

Another question to be clarified is whether the effects of exercise during pregnancy can be sustained into adulthood. In this regard, Robinson and Bucci (2014) examined the effect of voluntary wheel running during the gestational period in adult offspring. Improvement in object recognition memory was

observed in progenies from 60 to 88 days of age. In another study, treadmill running during pregnancy promoted enhanced cognitive function (habituation behavior and spatial learning) in adult offspring (Gomes da Silva et al., 2016), indicating that exercise during the peri-natal period may increase brain function in offspring in adult life. Therefore, positive early life experiences such as physical exercise during the gestational period may persist in offspring and may consequently play an important role in increasing brain resilience in later life.

Neurobiological Mechanisms

Considering that few studies in humans have examined the effects of physical activity during pregnancy on offspring's neurodevelopment, the mechanism by which exercise during pregnancy impacts on progeny's cognitive function is just starting to be clarified. Two studies conducted by Clapp (1996) and Clapp et al. (1998) focusing on the first years of life (ages one and five), found no significant difference in the offspring's morphometric parameters (head circumference and height). In a more recent investigation, a better cerebral maturation in the newborn of exercised pregnant mothers was observed by means of a neurophysiological index of sound discrimination and auditory memory (the slow positive mismatch response—SPMMR) (Labonte-Lemoyne et al., 2017). The long-term effects of exercise during pregnancy on the offspring, i.e., in their adult life, still remain to be elucidated.

Unlike human studies, much more information has been collected from laboratory animals and several factors have been proposed on these effects. Prominent cell proliferation and survival in offspring following exercise during pregnancy have been observed (Bick-Sander et al., 2006). For instance, swimming (Lee et al., 2006) and treadmill running (Kim et al., 2007) from embryonic day 15–21, the late developmental stage of the rodent fetus, provoked an increase in the number of BrdU-labeled cells (marker of proliferating cells) on post-natal day 29 (P29) in the hippocampus, a region related to learning and memory, and this proliferative effect was associated with an improvement of cognitive function. Significant changes may also occur in later periods of life. Some studies have shown an increase in absolute numbers of neuronal and non-neuronal cells and brain-derived neurotrophic factor (BDNF) levels in the hippocampal formation of adult offspring (P60) (Gomes da Silva et al., 2016) and increased cell density in the hippocampal CA1 and CA3 areas during the adult period (P120) (Dayi et al., 2012) of offspring of mothers trained during the gestational period. Of note, increased BDNF levels in the hippocampal formation of pups of exercised mothers were associated with better spatial learning (Akhavan et al., 2008) and BDNF deletion resulted in learning deficits (Gorski et al., 2003). With regard to this, molecular systems, essentially involving BDNF, have been reported to play an important role in exercise-induced cognitive improvement. Overall, offspring of exercised mothers during pregnancy show increased neurogenesis, hippocampal BDNF mRNA and BDNF protein, and improved learning and memory throughout life (Lee et al., 2006; Kim et al., 2007; Gomes da Silva et al., 2016), indicating that increased BDNF expression induced by exercise during gestation may improve brain function in the offspring.

The results indicate that pre-natal exercise can induce long-term effects on the hippocampal plasticity of progeny (Dayi et al., 2012). These findings are of great importance because the hippocampal region contributes to long-term potentiation (LTP), one of the cellular mechanisms required for learning and memory (Bliss and Collingridge, 1993). It is well-known that activation of the N-methyl-D-aspartate (NMDA) glutamate receptor generates LTP, as well as learning and memory. In this context, better performance in the Morris water maze tests was observed in pups of trained mothers during pregnancy compared with pups of sedentary mothers and this effect was abolished by the NMDA antagonist MK-801 (Akhavan et al., 2008). In addition to the cognitive effects, there is supportive evidence that exercise during pregnancy exerts a neuroprotective effect in the progeny. In the study by Herring et al. (2012), voluntary wheel running during pregnancy reduced beta-amyloid plaque burden, APP processing, oxidative stress, inflammation, and neurovascular dysfunction in offspring at 5 months of age, suggesting that pre-natal physical activity may also contribute to reducing the future risk of neurological diseases.

Physical Exercise in Childhood and Adolescence

In relation to exercise interference in post-natal brain development, i.e., during infancy or adolescence, numerous human studies have reported positive findings in cognitive functioning following acute (Hillman et al., 2009; Ellemberg and St-Louis-Deschênes, 2010) or chronic physical exercise (Hillman et al., 2005, 2014). A meta-analysis of 16 studies showed a positive association between cognition (learning and intelligence scores) and physical activity in school-age children (Sibley and Etnier, 2003). A superior performance in three stroop conditions (attention tasks) was observed in children between seven and 12 years of age with better aerobic fitness (Buck et al., 2008) and in arithmetic cognition in fitter pre-adolescent children aged nine–ten (Moore et al., 2014). An elegant investigation conducted by a Swedish group who evaluated 1,200,000 adolescents showed a positive association between physical fitness and better cognitive performance at age 18 years and occupational status and educational achievement later in life (Aberg et al., 2009). A further important consideration is whether regular physical activity during adolescence or adult life promotes long-lasting cognitive effects. In the study by Dik et al. (2003), physical activity at 15 and 25 years induced better cognitive performance at 62 and 85 years of age. These findings indicate that regular physical activity in early life is able to improve cognitive functioning, supporting the cognitive reserve hypothesis. Although very optimistic, confirmatory studies have yet to be conducted in further human studies.

While promising findings on the effects of exercise during infancy or adolescence have been well-documented, far less is known about its impact on brain resilience. Chronic stress during the adolescent period may impact negatively, both physically and psychologically (Sheth et al., 2017) and regular physical

activity may be of great value in adolescent stress management. For instance, Norris et al. (1992) conducted a retrospective and experimental study to examine the influence of physical activity and an exercise program on psychological stress and well-being in adolescents. In their retrospective analysis, adolescents who engaged in exercise/sports activities more regularly reported less perceived stress and depression. In the second part of their study, a group of adolescents submitted to a regular exercise program reported significantly less perceived stress than their controls, suggesting that physically fit adolescents seem to be less susceptible to life stressors. In a recent cross-sectional survey (Kim et al., 2019), adolescents from 14 to 19 years old who engaged in physical activities more than five times per week were stressed less often than those who were involved in fewer physical activities. To indicate whether any psychological benefits would have been maintained, it would be reasonable to analyze a follow-up period at the end of the physical exercise program or physical activity. Of note, a cross-sectional study that examined the relationship between participating in physical activity at several time-points in life (teenage, age 30, age 50, and late-life) and late-life cognitive function showed that teenage physical activity was greatly associated with a lower probability of cognitive impairment in elderly people who were physically active (Middleton et al., 2010). However, the survey did not take account of whether cognitively impaired subjects had been through stressful life events. Thus, conditions other than a stressful early life may influence cognitive reserve in later life, such as nutritional status during childhood (Zhang et al., 2010) and education (Zahodne et al., 2015). Overall, these findings suggest that the cognitive reserve built up in physically fit subjects in the early stages of life prepare the brain to be more resilient to cognitive impairment, dementia, and consequently Alzheimer's pathology; this probably occurs through brain plasticity.

In addition to cross-sectional studies, we should note how long-term physical activity can impact in later life. A prospective 6-years follow-up study with 496 adolescent girls designed to examine the relationship between physical activity and mental health during adolescence showed a reduced risk for future depressive symptoms (Jerstad et al., 2010). In another prospective and retrospective analysis, physical activity during childhood and adolescence was associated with a reduced risk of depression 20 years later (McKercher et al., 2014). Subsequently, a long-term follow-up over a period of 14 years, using a large sample of subjects from adolescence through adult life (18–29 years old), showed that those engaged in higher levels of physical activity presented lower levels of depressive symptoms over time (from adolescence into adulthood) (McPhie and Rawana, 2015). Collectively, the scientific literature presents strong indicators that habitual physical/sport activities at an early age may boost lifelong brain function and may also reduce the risk of several brain disorders.

Similar findings have been found in laboratory animals. In a classic study conducted by Uysal et al. (2005), young rats submitted to treadmill exercise during adolescence and early adulthood (from post-natal day 22 to post-natal day 78; P22 to P78) presented better spatial memory in the water maze test compared to non-exercised rats during this period. Using another exercise model (voluntary wheel running) and a non-spatial form of learning and memory (object recognition memory), it was observed that rats with free access to wheel running from P25 to P55 had a better discrimination ratio between novel and familiar objects compared to their controls (Hopkins et al., 2011). Notably, 2 and 4 weeks after the exercise had terminated, exercised rats performed better in the re-test compared to their controls. Similar findings were observed in a study conducted by our research group (Gomes da Silva et al., 2012). Treadmill running during the adolescent period (P21–P60) resulted in improved spatial learning and memory tested at P60–P65, and, like the study by Hopkins et al. (2011), rats showed better spatial memories in later life (at P96) (Gomes da Silva et al., 2012). These findings also indicate that physical exercise during this critical period of brain development can result in sustained cognitive benefits, that is, in a neural reserve that can be useful in old age.

Neurobiological Mechanisms

Changes in function and brain structure are clearly associated with exercise-induced improvement in cognition early in life. Improved fronto-temporal white matter integrity, which is related to improved cognitive function, has been observed following 8 months of aerobic exercise in overweight 8–11 year-old children (Schaeffer et al., 2014). Greater hippocampal volume and better performance in relational memory were detected in fitter children compared to less fit children (Chaddock et al., 2010). Also, greater gray matter volumes in frontal, temporal, and subcortical areas were also related to higher cardiorespiratory fitness; and some regions such pre-motor cortex, supplementary motor cortex, and hippocampus were related to better academic performance (Esteban-Cornejo et al., 2017). On the electro-physiological level, positive changes in event-related brain potential that may underlie cognitive performance have been observed in pre-adolescents following an acute bout of treadmill walking (Hillman et al., 2009) or in fitter children (Moore et al., 2014). Other factors by which physical exercise can interfere beneficially for cognition include the release of growth factors such as BDNF, Insulin-like growth factor 1 (IGF-I), and vascular endothelial growth factor (VEGF), possibly providing reserve against later cognitive decline and dementia. These neurotrophins are produced and secreted in the brain and play an essential role in regulating proliferation, development, and cellular differentiation. For instance, an aerobic exercise program increased serum BDNF levels in adolescents, which was associated with better working memory (Jeon and Ha, 2017). A single bout of high-intensity, but not low-intensity, exercise was able to improve memory as shown by remembering more newly learned vocabulary words compared to the control group (Hötting et al., 2016). Supporting the above findings, a recent systematic review and meta-analysis reported significant results on the levels of BDNF and executive function in adolescents submitted to physical exercise (de Azevedo et al., 2019). Overall, the combined effects of neurotropic factors and physical exercise from childhood to adolescence, a critical window of brain development, may contribute to improvements in memory and also in various aspects of academic performance, consequently preventing or minimizing age-associated cognitive decline.

With regard to the results of animal studies during post-natal brain development, increased hippocampal cell proliferation was shown in rats trained over five consecutive days with 4-week-old (Kim et al., 2004) and neurogenesis in rats trained for one week from P29 to P35 (Lou et al., 2008). Our research group observed that increased hippocampal cell proliferation (stained with Ki67) induced by exercise occurred mainly in the earliest stages of post-natal development (de Almeida et al., 2013). In line with this, Uysal et al. (2005) reported an association between an increased number of hippocampal cells in CA1, CA3, and the dentate gyrus and better spatial memory in trained rats during development. Improvement in spatial memory was also related to increased axonal density of granule cells in the dentate gyrus stained by the Neo-Timm method in trained adolescent rats (Gomes da Silva et al., 2012). As highlighted previously, BDNF plays a potential role in the modulation of cognitive functions. To this end, higher BDNF mRNA (Abel and Rissman, 2013), BDNF expression, and its receptor tropomyosin-related kinase B (Gomes da Silva et al., 2012) have been detected in rats trained during adolescence, indicating that brain BDNF in early life induced by exercise may be associated with cognitive improvement.

Physical Exercise in Adulthood, Aging, and Neurological Disorders

As outlined, positive early life experiences or lifestyle factors such as physical exercise have been associated with resilience in later life, suggesting that regular exercise can generate brain protection by means of reserve. For adult, middle-aged or aged people, physical exercise is frequently recognized to slow cognitive decline and protect against the consequences of stressful events. For instance, the practice of physical exercise in mid-life (from age 25–50) was able to reduce the chance of dementia in older adults (Andel et al., 2008) and improve cognition, mainly for executive-control processes (Colcombe and Kramer, 2003).

Despite the growing number of positive findings relating exercise and cognition in adulthood and aging, some prospective longitudinal studies have reported null results (Broe et al., 1998; Wilson et al., 2002). In the study by Broe et al. (1998), no association was found between exercise and cognitive performance, and in another survey, cognitive but not physical activities were associated with a reduced risk of cognitive decline (Wilson et al., 2002). We have to bear in mind that mixed findings related to the effect of physical activity in cognition can be partly attributed to cognitive reserve. Sánchez Rodríguez et al. (2011) used factor scores to assess cognitive reserve, classifying the participants into high or low reserve. Patients with Alzheimer's disease (AD) with low cognitive reserve scores presented more deficits in neuropsychological tests such as memory, attention, and language than patients with high cognitive reserve. Higher education, higher professional performance, and ludic activities were factors contributing to cognitive reserve and physical activity was not considered a factor for cognitive reserve in their study. Similarly, Fritsch et al. (2007) found educational level but not physical and social activities to be predictors of cognitive function in the elderly.

The above studies suggested that although the cognitive reserve is influenced by intrinsic differences or during childhood, stimuli at later periods of life can also positively or negatively alter the reserve. Thus, some variables such lifestyle habits, age, different follow-ups, physical exercise habits, or types of exercise intervention are confounders that can interfere with the studies' outcomes. To deal with any research gaps, a growing number of meta-analyses have been conducted to verify the impact of physical activity in the adult or elderly population. For instance, individuals aged $\geq$40 years with better levels of physical activity presented lower risk of cognitive decline and dementia (Blondell et al., 2014). An investigation by Hamer and Chida (2009) using a meta-analysis of prospective studies found that habitual physical activity was able to reduce by 28% and 45% the risk of dementia and the risk of AD, respectively. In a more recent meta-analysis, exercise duration of 45–60 min per session and of moderate or vigorous intensity was associated with improvement in cognition function in subjects older than 50 years (Northey et al., 2018). Since age is the main risk factor for dementia, particularly Alzheimer's, sustained physical/sports activities have been associated with reduced incidence of AD and therefore increased resilience against developing AD (Rovio et al., 2005; Lautenschlager et al., 2008).

Studies have demonstrated that psychological stress and other psychosocial factors such depression increase vulnerability to AD (Mejía et al., 2003; Aznar and Knudsen, 2011; Yuede et al., 2018) and regular physical exercise plays an important role in stress management and increased resistance to stress-related disorders (Tsatsoulis and Fountoulakis, 2006). Although studies have examined the effects of stress or physical exercise on AD independently, the interaction of stress and exercise needs to be better explored. To this end, a review by Yuede et al. (2018) reported attractive findings from pre-clinical studies on this interface.

AD has also been associated with the occurrence of cerebrovascular disease and physical exercise plays a positive role in this condition (Lange-Asschenfeldt and Kojda, 2008). Physical exercise of moderate intensity increases cerebral blood in humans (Braz and Fisher, 2016), which could minimize the effects of hypoperfusion in AD. Hypotheses by Nation et al. (2011) have been formulated concerning the impact of exercise and stress on the cerebrovascular system with increased risk of developing AD, highlighting preventive strategies for this disease.

In addition to the preventive effect described above, physical activity/exercise has been demonstrated to promote neurobiological benefits for brain pathology, consequently attenuating the decline in AD. Authors such Hoffmann et al. (2015) demonstrated that a supervised exercise program over 16 weeks was able to delay neuropsychiatric symptoms in patients with mild AD. In a subsequent investigation from the same research group, using the same exercise protocol, a positive correlation was found between frontal cortical volume and measures of mental speed and attention (Frederiksen et al., 2018). Cardiorespiratory fitness, as measured by maximal oxygen consumption (VO2max), has been associated with cognition (Wendell et al., 2014) and this evidence has also been reported in patients with AD (Vidoni et al., 2012). In line with this, a study

analyzing a direct measure of VO2max in patients with mild AD detected a positive connection between VO2 peak, cognition, and neuropsychiatric symptoms (Sobol et al., 2018). In sum, an increasing number of studies have reinforced the role of exercise in minimizing the reduced cognitive function in AD (Groot et al., 2016).

In animals, extensive literature has shown a positive association between exercise and cognition in adulthood and aging, supporting the important role of exercise in brain health as demonstrated here. Classic studies by van Praag et al. reported that voluntary wheel running improved hippocampus-dependent learning and memory in young adult (van Praag et al., 1999) and aged mice (van Praag et al., 2005). Similar findings have also been demonstrated in other exercise protocols. Results from forced and voluntary exercise showed improved short-term and spatial memories in young and old rats (Kim et al., 2010; Speisman et al., 2013) and resistance exercise improved performance in the passive avoidance test, a hippocampus-dependent memory task, in young adult rats (Cassilhas et al., 2012). With regard to whether exercise can impact positively in stressful conditions, a recent study showed that impaired cognition induced by chronic stress in mice was prevented in stressed animals submitted to regular moderate and intense exercise (Lee et al., 2018). This adaptive effect of regular exercise on the homeostatic system can improve resistance and/or resilience to physical and psychological stress and may consequently protect against brain disease. To this end, exercise can play an important role in increasing resistance to stress in AD. An elegant review by Yuede et al. (2018) reported findings from studies of different exercise protocols in AD mouse models and discussed the interplay between stress and exercise in AD. Although research has focused on the effects of aerobic exercise (forced or voluntary exercise) in AD models (Nichol et al., 2007, 2008; Xiong et al., 2015), less is known about the impact of resistance exercise on this pathology. Our group and others have recently shown that resistance exercise may minimize the alteration in exploratory activity (Hashiguchi et al., 2020) and in cognitive function (Liu et al., 2020) in a transgenic mouse model for AD.

Neurobiological Mechanisms

As with pre-adolescents and adolescents, changes in brain structure and function and improvement in several aspects of cognition have been observed in the adult population as result of better cardiorespiratory fitness. A meta-analysis conducted by Kramer and Colcombe (2018) has elegantly highlighted this issue. In younger adults, a 6-weeks exercise program was able to increase hippocampal volume (Thomas et al., 2016). In older subjects, 6 months of aerobic program (walking) induced increases in volume in frontal and temporal gray matter and white matter regions (Colcombe et al., 2006) and similar effects were reported by other studies (Erickson et al., 2011; Reiter et al., 2015). Although cardiorespiratory fitness induced by conventional physical training such as walking, jogging or cycling has been extensive reported to promote brain plasticity, a study conducted by Rehfeld et al. (2018) showed that dance training produced larger brain volumes compared to repetitive exercise in the elderly. Indeed, a recent systematic review highlights the impact of dance practice to induce brain plasticity (Teixeira-Machado et al., 2018).

Concerning white matter integrity, increases were reported in temporal and parietal regions in older subjects submitted to 1 year of an aerobic exercise program (Voss et al., 2013). Of note, better cardiorespiratory fitness in young and older adults has also been related with increases in hippocampal cerebral blood volume and memory improvement (Chapman et al., 2013), supporting the idea that regular exercise may build a vascular reserve against AD. With respect to neurotrophic factors, a link between BDNF, exercise, and cognition has been proposed during aging, suggesting that this association may have a critical role for the prevention and minimization of cognitive impairment during aging (Wang and Holsinger, 2018). Indeed, some authors have elegantly emphasized physical exercise as a means of restoring BDNF in this neurological condition, a finding that is also supported by animal studies (Wang and Holsinger, 2018). Essentially, aerobic fitness and serum BDNF levels in older adults have been correlated with increased hippocampal volume and better memory (Chaddock et al., 2010; Erickson et al., 2011). While the existing literature indicates the positive association of exercise and BDNF on cognition, further investigations are necessary in elderly and neurological subjects.

In pre-clinical studies, positive associations between exercise and cognition in adulthood and several possible neurobiological mechanisms have been proposed for the improvement of cognitive reserve. Extensive literature has reported that exercise can increase adult hippocampal neurogenesis (for a review see van Praag, 2008) and hypothalamus-pituitary-adrenal axis regulation (Wang et al., 2014), suppress apoptosis (Kim et al., 2010), reduce oxidative stress and mitochondrial dysfunction, modulate cytokine signaling (Speisman et al., 2013), increase vascular density (Ding et al., 2006) and production of BDNF and IGF-1 (Vaynman and Gomez-Pinilla, 2005), alter brain morphology (Stranahan et al., 2007) and electrophysiological properties of neurons (van Praag et al., 1999). These findings on brain plasticity induced by exercise are believed to support the improvement in learning and cognitive function.

The above-mentioned mechanisms revealed to be induced by exercise in the healthy population to improve cognitive performance could also be applied in aging and neurological disorders. In AD, some proposed mechanisms in mice models include increased BDNF expression, reduced inflammation, reduced amyloid deposition and phosphorylated tau accumulation (for a review see McGurran et al., 2019). For instance, reduced oxidative stress and Aβ scores were related to better working memory using three types of exercise for 6 weeks (aerobic, resistance, and combined exercises—aerobic + resistance) (Özbeyli et al., 2017).

Exercise in Other Neurological Disorders

Besides the neuroprotective effects against aging, and an extensive number of studies looking at the prevention or minimizing of cognitive decline and dementia, regular physical exercise has had a positive influence in other neurological diseases. Here, we will focus on some common neurological disorders such Parkinson's, Epilepsy, and Stroke.

Parkinson's Disease (PD)

PD is the second most common neurodegenerative disease worldwide, affecting 1% of the elderly population. A considerable number of scientific studies have highlighted the role of exercise in reducing the risk of PD, highlighting its contribution to resilience in PD. Moderate to vigorous physical sport/activities including tennis, biking, swimming, heavy housework in mid- to later life have been associated with a lower risk of PD (Xu et al., 2010). Of note, in a prospective study, the intensity of physical activity was an influential factor for better resilience in PD. Vigorous, but not moderate, physical activity was related to a 50% lower risk of PD in men (Chen et al., 2005). Thus, an elegant cross-sectional large-scale study with 9,676 elderly participants reported physical exercise as the best protective factor against PD (Zou et al., 2015). More recently, a large meta-analysis of more than half a million adults reported an association between high levels of moderate to vigorous activity and low risk of developing PD (Fang et al., 2018). Interestingly, while Yang et al. (2015) found that a medium level of daily total physical activity lowered the risk of Parkinson's disease, Logroscino et al. (2006) did not support the finding that physical activity protects against PD. As pointed out by Yang et al. (2015), to evaluate physical activity/exercise level, epidemiological studies have utilized different activities to measure moderate to vigorous exercise, such as leisure time, household, or energy expended on physical activity in kilocalories per week, which can produce different outcomes. Therefore, one must be cautious when analyzing these outcomes.

Although there is beneficial evidence of a decrease in the risk of PD, the influence of physical exercise in slowing the progression of the disease has not been completely explored. From few clinical trials, positive effects have been observed in PD resilience. Robottom et al. (2012) demonstrated that resilience in PD was associated with better health-related quality of life and reduced disability and non-motor symptoms (less apathy, depression, fatigue). Improvement in motor symptoms and physical functioning in people with PD was reported in a review which focused on the long-term effects of exercise (duration lasting at least 12 weeks) (Mak et al., 2017). Besides the classical motor symptoms, behavioral and cognitive symptoms are common in PD and positive results from exercise programs in several cognitive domains have been found in the literature (da Silva et al., 2018). Authors have reported improvement in the executive functions after aerobic (Altmann et al., 2016) or resistance training (Silva-Batista et al., 2016). With regard to the concept that resilience is an active process, the reduced disability and non-motor symptoms observed in PD could be minimized through regular physical exercise.

Regarding pre-clinical data, a number of studies have indicated that different types of aerobic exercise can improve cognitive function in PD. This positive effect has been investigated in exercise training applied before, during, and after parkinsonism-inducing treatment. Exercise can enhance the memory of rats by reducing cognitive impairment in a treadmill or swimming exercise protocol (Goes et al., 2014; Viana et al., 2017). In a voluntary exercise protocol, short-term exercise was effective in reducing cognitive deficits and depressive behavior and long-term exercise minimized the progression of motor symptoms (Hsueh et al., 2018; Mul et al., 2018).

Neurobiological Mechanisms

In PD, limited information on neurobiological mechanisms has been reported in humans. Growing evidence suggests that physical exercise can minimize dopaminergic neuronal damage within basal ganglia motor circuits. In an *in vivo* study, the availability of the dopamine transporter by using [11C]CFT was reduced in the putamen after 1 h of strenuous walking in normal subjects but not in PD patients, indicating that this abnormal activation might be linked to the pathophysiology of the parkinsonian gait (Ouchi et al., 2001). In this regard, BDNF exerts an important influence in the mesolimbic dopaminergic pathway and altered BDNF levels have been observed in PD pathology. In post-mortem analysis, reduced expression of BDNF protein was observed in the *substantia nigra pars compacta* of PD patients compared to control subjects (Parain et al., 1999). Thus, blood analysis showed decreased serum BNDF levels in PD patients when compared with controls (Scalzo et al., 2010). In line with this, a systematic review and meta-analysis reported reduced serum BDNF levels in PD patients compared to healthy controls in spite of the presence of co-morbidities such depression among non-depressed and depressed PD patients (Rahmani et al., 2019). The physiological mechanisms of BDNF changes induced by exercise have been proposed in a systematic review and meta-analysis which reported increased BDNF blood levels following a physical exercise program in PD patients (Hirsch et al., 2018). In sum, the mechanisms and possible directions for neuroprotection in PD have been significantly explored, but more research is needed on the influence of exercise in this scenario in humans.

Pre-clinical investigations have revealed important effects of exercise on the nigrostriatal pathway, resulting in increasing extracellular dopamine release and reduction of striatal dopamine loss terminals (Petzinger et al., 2013). In part, these benefits are supported to facilitate DA neurotransmission and some studies support these affirmations. For instance, 4 weeks of swimming prevented the decrease of dopamine and its metabolites DOPAC and HVA levels induced by 6-OHDA in the striatum of mice and restored long-term memory in the object recognition test (Goes et al., 2014). Moreover, 2 weeks of treadmill reduced nigrostriatal dopaminergic cell loss, increased cell proliferation in the hippocampal dentate gyrus, and minimized short-term memory impairment in 6-OHDA-induced Parkinson's rats (Cho et al., 2013).

Epilepsy

Epilepsy is another common neurological condition affecting over 70 million people worldwide. It is characterized by an enduring predisposition to generate spontaneous epileptic seizures, presenting several neurobiological, cognitive, psychological, and social consequences (Fisher et al., 2014). A number of factors such seizure control and reduced depression and anxiety can impact positively on the quality of life of people with epilepsy. These protective factors could be characterized as resilience in the context of epilepsy. Thus, regular exercise over

the life course has been associated with resilience to developing epilepsy. In this scenario, some human investigations have explored whether previous physical exercise practice is able to reduce the incidence of epilepsy. For instance, a large and population-based cohort, consisting of 1,173,079 men, over a long observation period (up to 40 years) by a Swedish group showed that low cardiovascular fitness evaluated at age 18 was associated with a risk of presenting epilepsy later in life (Nyberg et al., 2013). Reinforcing the above finding, a more recent study conducted by Ahl et al. (2019) compared the incidence of epilepsy over 20 years in a large number of participants of a long-distance Swedish cross-country ski race (Vasaloppet) with the incidence of their match controls in a register of the Swedish population. They found up to 40–50% lower incidence of epilepsy in cross-country ski racers before retirement. Notably, data sub-analyses demonstrated that faster ski racers had a significant lower incidence of epilepsy compared to those with a slower finishing time. Both above findings are indicative that regular physical exercise and better physical fitness can be protective against developing epilepsy.

Physical exercise also plays a positive role after epilepsy is established. Factors such as social functioning, ability to work, stigma, prejudice, and adjustment to seizures significantly reduce the quality of life of people with epilepsy and are generally associated with depression and anxiety disorders. From the limited number of prospective studies in humans, a reduced number of seizures, reduced anxiety and depression symptoms, improvement of quality of life together with better capacity to cope with stress are observed after exercise programs (Bjorholt et al., 1990; Roth et al., 1994; McAuley et al., 2001; Vancini et al., 2013). Certainly, physical exercise has been suggested as a potential candidate for stress reduction in people with epilepsy (Arida et al., 2009). The influence of exercise on the reduction in seizure frequency or seizure susceptibility is an important factor in this picture. Seizure frequency has been negatively associated with cognitive function (Tromp et al., 2003; Hoppe et al., 2007). It has been demonstrated that people with temporal lobe epilepsy, the most common form of epilepsy, with low seizure frequency presented better performance on tests of anterograde memory compared to those with high seizure frequency (Voltzenlogel et al., 2014). In line with this, clinical studies have reported that physical exercise programs improve seizure control (Eriksen et al., 1994; Nakken, 1999). However, the influence of physical exercise on cognition is poorly investigated. To our knowledge, only two studies have explored the influence of an exercise program on cognition in people with epilepsy. Children with benign epilepsy submitted to ten supervised exercise sessions for 5 weeks showed significant improvements in attention tests (Eom et al., 2014). Although this is an encouraging result, the study presented a small sample, no control group, and only a short period of exercise intervention. Thus, most of them were seizure-free and receiving monotherapy. In a recent randomized study, adults with epilepsy submitted to 12 weeks of a combined exercise program presented an improvement in some domains of cognitive function such attention and language tasks (Feter et al., 2020). Although further research in humans is needed, the efficacy of exercise programs in improving cognitive functions in animal models of epilepsy have been very positive and play a beneficial role in increasing resilience to developing epilepsy.

Findings concerning exercise and cognition have been positive in different models of epilepsy. For instance, a 30-days swimming exercise reduced learning and memory deficits in rats submitted to a kainite acid model (Gorantla et al., 2016). Two types of exercise, voluntary wheel running and swimming, reduced seizure frequency and improved cognitive performance, measured by the object recognition test and the passive avoidance test (Lin et al., 2019). Recently, we demonstrated that resistance exercise was able to decrease the number of seizures, which was associated with a reduction in memory impairment (de Almeida et al., 2017). Promising results have been found with regard to investigations about the effects of exercise on cognitive changes in animals submitted to *status epilepticus* earlier in life. Rats submitted to penicillin-induced recurrent *epilepticus* in early life and then exercised during the final period of adolescence (P49-P54) presented better performance in the water maze test than their controls (Ni et al., 2009). In addition, cognitive impairments induced by lithium-pilocarpine-induced *status epilepticus* at weaning was decreased in animals housed in environmental enrichment with wheel running (Fares et al., 2013). Thus, an exercise program in rats conducted during the period of post-natal brain development reduced seizure susceptibility later in life, indicating that exercise undertaken in early life may build a neural reserve against brain disorders (Gomes da Silva et al., 2011). The authors suggest that physical exercise during early periods of life may provide an adequate development of neural circuitry, which can support greater brain damage in later life. Collectively, these studies reinforce the neuroprotective and rehabilitative influence of exercise in epilepsy.

Neurobiological Mechanisms

With epilepsy, we can only make suppositions regarding the effects of exercise in humans. Some possible mechanisms are modulation of the neurotransmitter system and changes in metabolic, neuroendocrine, and growth factors. Cellular and molecular events underlying epilepsy can impair growth factor signaling in the brain and current evidence has associated BDNF with the pathophysiology of epilepsy in humans. Increased levels of BDNF have been found in the surgically resected temporal neocortex (Takahashi et al., 1999) or hippocampus of patients with TLE, demonstrating that epileptic activity may increase BDNF levels and its gene expression (Murray et al., 2000). Conversely, in the periphery, decreased levels of plasma (LaFrance et al., 2010) and serum BDNF have been reported in adult patients with epilepsy (Hong et al., 2014). Considering that regular exercise has been known to reduce neuroinflammation, oxidative stress, and excitotoxicity (Moylan et al., 2013), it can be suggested that exercise might modulate these effects in this condition, therefore building brain resilience against epilepsy.

Although there is no reported effect in epilepsy patients, positive outcomes have been found in animal models of epilepsy. Modulation of excitatory/inhibitory systems and neurotrophic factors has been demonstrated in several epilepsy models. Reduced levels of synaptic-related proteins and GABAergic function in epileptic animals were reversed by exercise, which

was associated with improved cognitive function and reduced seizure frequency (Lin et al., 2019). Recently, we examined the influence of exercise on the activation of downstream proteins related to BDNF-TrkB receptor. Aerobic exercise increased hippocampal BDNF expression, restored the overexpression of full-length TrkB and truncated-TrkB isoforms to control levels, and altered the hippocampal activation of some proteins linked to BDNF-TrkB intracellular signaling (de Almeida et al., 2018) and resistance exercise restored to control levels the altered BDNF levels and ERK and mTOR activation in rats with epilepsy (de Almeida et al., 2017). Thus, improved learning and memory in rats with epilepsy housed in an enriched environment with wheel running was accompanied by increased hippocampal neurogenesis and BDNF and VEGF transcripts (Fares et al., 2013).

Stroke

Stroke is the second leading cause of mortality and the principal cause of physical disability around the world. Despite extensive efforts, the development of preventive or rehabilitative treatment has not been totally effective (Moskowitz et al., 2010). Among therapies for this condition, physical activity/exercise has been proposed in a large number of investigations. The literature shows that regular practice of physical exercise is inversely related to stroke risk. Not only in stroke prevention, but also in stroke recovery in physical and cognitive tasks (Han et al., 2017).

A large amount of research has reported an inverse association between cardiorespiratory fitness and stroke. In one investigation of 16,000 men, those with moderate or high fitness presented lower risk of stroke mortality compared to low fitness individuals (Lee and Blair, 2002). In another large cohort study with women during a mean follow-up of 11.9 years, walking was related with lower risks of total, ischemic, and hemorrhagic stroke (Sattelmair et al., 2010). In accordance with the above findings, a meta-analysis by Lee et al. (2003) found that active individuals presented lower risk of stroke incidence and between the two categories of active subjects, moderately active and highly active, individuals had a 20 and 27% lower stroke risk, respectively, than the low active subjects. Although vigorous exercise is more effective, it seems that people who usually exercise at moderate levels can also see some benefit in preventing stroke. Considering that participating in moderate activity applies to the much of the population, this issue may be better explored in future studies.

The benefits of exercise have also been supported by various studies in individuals who have had a stroke. For instance, there is robust evidence for the beneficial effects of exercise on improving cardiorespiratory fitness and mobility after stroke. This evidence is based on a Cochrane Systematic Review which included 2,797 participants from 58 studies to examine the influence of physical exercise on stroke recovery (Saunders et al., 2016). The supportive effect of exercise on rehabilitation post-stroke has also been documented in clinical guidelines (Billinger et al., 2014). In addition to the above benefits, improvement in cognitive function has been reported in several controlled trials applying structured physical training to stroke patients (Blanchet et al., 2016; Ihle-Hansen et al., 2019). A meta-analysis of randomized controlled trials selecting studies with a duration of training >4 weeks showed a positive impact of exercise on some measurements of cognitive performance such as attention/processing speed following a stroke (Oberlin et al., 2017). Taking into account that studies address different or combined interventions, i.e., different inclusion criteria across the studies such as physical activity (leisure time or recreational activity), exercise program or cardiorespiratory fitness, a study conducted by Brouwer et al. (2019) evaluated the influence of solely aerobic training on vascular and metabolic risk factors for stroke. A beneficial effect on systolic blood pressure and fasting glucose was observed after stroke compared to non-aerobic exercise. More investigations using physical training programs will provide a better perception of this intervention (aerobic exercise) for improving resilience to stroke. With this in mind, higher levels of physical activity and exercise are important factors in reducing the risk for cardiovascular diseases and consequently increasing resilience for stroke.

In addition to physical disability and cognitive impairments, social factors are also common in stroke patients, notably changes in depressive symptoms, and social desirability. In a survey with stroke survivors, feelings of depression, fatigue, and low motivation were found to be factors that reduced the desire to undertake physical activity, while self-determination and goal achievement were related with greater involvement in physical activities (Morris et al., 2012). Therefore, healthy habits early or during the life course might influence healthier behaviors and cognitive recovery after stroke.

In general, animal models of stroke have confirmed that aerobic exercise of moderate intensity seems to be beneficial to cognition. Indeed, increasing reports have indicated that early exercise is protective against stroke (Zhang et al., 2015) and can minimize memory impairment induced by ischemic brain injury (Sim et al., 2004, 2005). For instance, 2 weeks of aerobic exercise introduced 24 h after middle cerebral artery occlusion significantly induced spatial memory recovery (Yang et al., 2017). Although these are positive findings, it is important to note that the intervention time window and exercise intensity are critical to the outcome. In this regard, some studies have reported that low-intensity exercise induces better effects on a spatial learning task in a water maze test and on both object recognition and location tasks than high-intensity exercise (Shih et al., 2013; Shimada et al., 2013). Overall, animal data suggest that physical exercise plays a role in cognitive function, thereby enhancing cognitive reserve. With regard to pre-stroke, although there is little information on cognitive effects, animal studies have clearly demonstrated that pre-ischemic exercise may minimize stroke severity in functional motor outcomes (Ding et al., 2004).

Neurobiological Mechanisms

Several mechanisms by which physical exercise exerts an effect in the prevention of and recovery from stroke are similar from those observed in the neurological diseases mentioned above. Acute ischemic stroke patients reporting a high level of physical activity prior to stroke were associated with greater VEGF expression and good outcomes after stroke (López-Cancio et al., 2017).

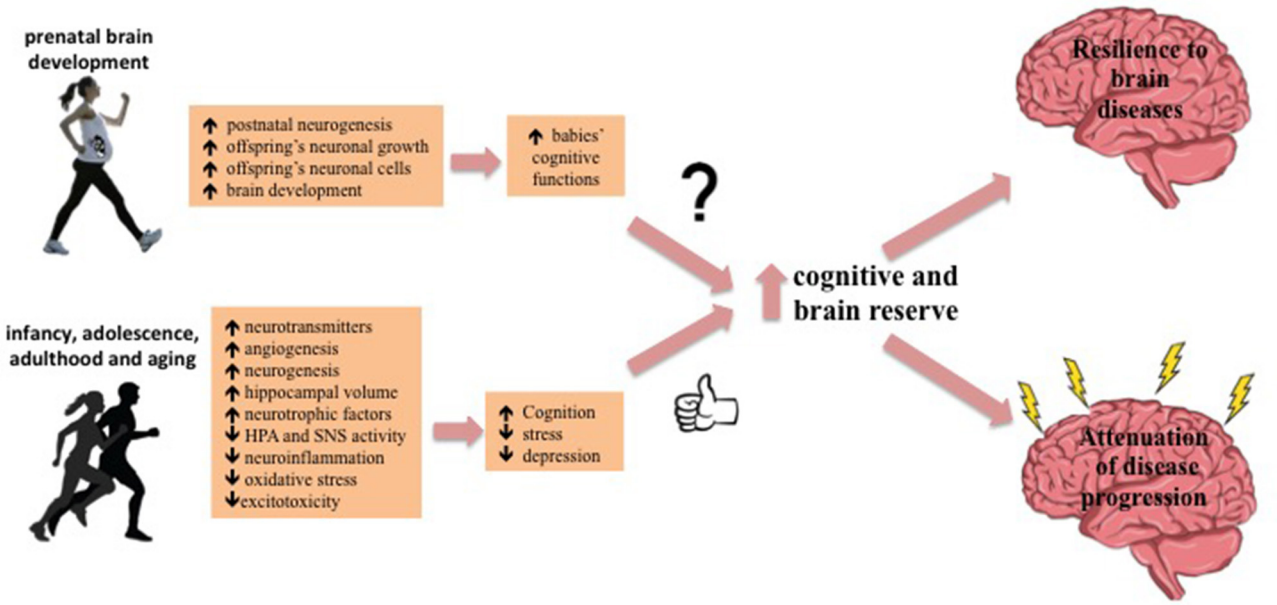

FIGURE 2 | Model of how exercise can confers brain resilience. Exercise positively influences brain and cognitive reserve by multiple pathways, protecting against the consequences of stressful events, improving health, and reduce the risk of chronic disease.

Many pre-clinical studies have examined the possible role of physical exercise in pre-conditioning and tolerance to cerebral ischemia. Exercise pre-conditioning-induced neuroprotection is mediated by multiple processes, such as maintenance of the integrity of the blood-brain barrier, anti-inflammatory effects, neovascularization, neurogenesis, and reduced excitotoxicity (Islam et al., 2017). For instance, data from animal models with cerebral ischemia or stroke submitted to exercise training have demonstrated positive neuroplasticity resulting in better cognitive performance, which can be attributed to increased expression of BDNF, synapsin-I, and post-synaptic density protein 95 (PSD-95) (Shih et al., 2013). Consistent with findings reported in health and in different brain diseases, it is supposed that BDNF plays an import role in this process because the improvement in spatial learning induced by exercise is reduced after the TrkB-BDNF receptor is blocked (Griesbach et al., 2009). Furthermore, better cognition in exercised animals has been associated with increased neurogenesis after cerebral ischemia (Luo et al., 2007) and increased antioxidant enzyme activity in the hippocampus in rats with bilateral common carotid artery occlusion (Cechetti et al., 2012). In sum, the pre-clinical findings clearly demonstrate that exercise has an important effect on metabolic and neurotrophic influences, which can explain its role in brain health and supportive action in terms of both resilience to and prevention of stroke.

CONCLUSION

Nowadays, we are constantly bombarded by media, physicians, and other health professionals to engage in physical/sports activities to reduce physical/psychological stress, improve our health, and reduce the risk of chronic disease. The literature has clearly demonstrated aerobic fitness as one of the best indicators of resilience. This is supported by evidence from a number of studies showing that physical fitness confers physiological and psychological benefits and protects against the development of stress-related disorders, as well as improves cognition and motor function that are a consequence of aging and of neurological disorders. Although we have learned about neurobiological mechanisms of physical fitness from the neuroplasticity and neuroprotection that confer resilience, these effects and mechanisms are diverse and complex and need to be further explored. However, we can summarize that exercise modulates several mechanisms that may increase brain health and counteract brain disorders (**Figure 2**). Exercise positively influences neuronal reserve by increasing BDNF expression which promotes neurogenesis and synaptic plasticity, reduces oxidative stress and inflammation, and enhances cerebral and peripheral blood flow, which stimulates angiogenic factors that lead to positive changes in the structure and morphology of brain vasculature. All these changes shape brain activity and serve as a buffer against stress-related disorders. Positive findings have also been observed concerning the effects of exercise on cognition and therefore cognitive reserve. However, several null findings, not reported here, should be analyzed with caution because different types of exercise intervention are confounders that can interfere with the studies' outcomes. The influence of exercise variables includes the duration, frequency, intensity, and length of exercise. To this point, several exercise regimens have been used to determine the optimal stimulus on brain resilience. However, the evidence for dose-response relationship

between exercise and brain/cognitive reserve in different life stages is not well comprehensive. Research investigating different dose-parameters of exercise both in animal and human has generated inconsistent results. These conflicting results may be partially attributed to the diversity of classifications used for high or low exercise intensity, volume and type (aerobic or resistance or anaerobic) of exercise that can be beneficial for brain resilience (Wipfli et al., 2008; Vidoni et al., 2015; Kramer and Colcombe, 2018; Greene et al., 2019). For older population, a systematic review and meta-analysis reported that healthy subjects should perform both aerobic and anaerobic exercises, of moderate intensity, for at least three times per week and those with cognitive impairments, exercise with shorter duration and higher frequency to obtain better cognitive outcomes (Sanders et al., 2019). In general, the American College of Sports Medicine recommendations should be applied (ACSM American College of Sports Medicine, 2013).

While several models of physical activity or exercise may impact positively on brain resilience such yoga, dance, martial arts, etc., in this review we aimed to focus mainly on the effects of aerobic exercise of low and moderate intensity or resistance exercise. Thus, physiological markers including heart rate variability, blood pressure and cortisol might be regularly used as indicator of stress to determine the impact of exercise on brain resilience. Some examples of stress systems are the immune-inflammatory system, the HPA—axis and the autonomic nervous system (Meggs et al., 2016). Disturbance of these systems could lead to hyperactivity of the HPA-axis, sympathetic activation and systemic inflammation. However, there are still unanswered questions concerning (1) whether physical exercise in early life can prevent or delay cognitive decline in later life, (2) the effectiveness of exercise programs for individuals across the life span and for those with neurological diseases, and (3) how much exercise is necessary to gain beneficial effects on cognitive health. This is a field of research that deserves more attention. Thus, it is unquestionable that multiple interacting factors, not explored in this review, including nutritional status and the link between genes and environment, mediated by epigenetic changes that occur at critical periods of development may confer vulnerability or resilience to brain disorders. Overall, this review provides an insight into the current evidence of physical exercise's contribution to the increase in resilience and brain tolerance to aging, pathology, and insult.

AUTHOR CONTRIBUTIONS

RMA and LTM participated in the design of the work, the bibliographic review and writing of the manuscript. Both authors approved the submitted version.

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Chronic Isolation Stress Affects Central Neuroendocrine Signaling Leading to a Metabolically Active Microenvironment in a Mouse Model of Breast Cancer

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Social isolation is a powerful stressor capable of affecting brain plasticity and function. In the case of breast cancer, previous data indicate that stressful experiences may contribute to a worse prognosis, activating neuroendocrine and metabolism pathways, although the mechanisms underlying these effects are still poorly understood. In this study, we tested the hypothesis that chronic isolation stress (IS) may boost hypothalamic–pituitary–adrenal (HPA) axis activity, leading to changes in the hypothalamic expression of genes modulating both mood and metabolism in an animal model of breast cancer. This centrally activated signaling cascade would, in turn, affect the mammary gland microenvironment specifically targeting fat metabolism, leading to accelerated tumor onset. MMTVNeuTg female mice (a model of breast cancer developing mammary hyperplasia at 5 months of age) were either group-housed (GH) or subjected to IS from weaning until 5 months of age. At this time, half of these subjects underwent acute restraint stress to assess corticosterone (CORT) levels, while the remaining subjects were characterized for their emotional profile in the forced swimming and saccharin preference tests. At the end of the procedures, all the mice were sacrificed to assess hypothalamic expression levels of Brain-derived neurotrophic factor (*Bdnf*), Neuropeptide Y (*NpY*), Agouti-Related Peptide (*AgRP*), and Serum/Glucocorticoid-Regulated Protein Kinase 1 (*SgK1*). Leptin and adiponectin expression levels, as well as the presence of brown adipose tissue (BAT), were assessed in mammary fat pads. The IS mice showed higher CORT levels following acute stress and decreased expression of *NpY*, *AgRP*, and *SgK1*, associated with greater behavioral despair in the forced swimming test. Furthermore, they were characterized by increased consumption of saccharin in a preference test, suggesting an enhanced hedonic profile. The IS mice also showed an earlier onset of breast lumps (assessed by palpation) accompanied by elevated levels of adipokines (leptin and adiponectin) and BAT in the mammary fat pads. Overall,

these data point to IS as a pervasive stressor that is able to specifically target neuronal circuits, mastered by the hypothalamus, modulating mood, stress reactivity and energy homeostasis. The activation of such IS-driven machinery may hold main implications for the onset and maintenance of pro-tumorigenic environments.

Keywords: social isolation stress, HPA axis, NPY/AgRP, leptin, brown adipose tissue, depression, mouse model, breast cancer

INTRODUCTION

Breast cancer is one of the most common cancers among women and a leading cause of mortality with over 2 million new cases worldwide diagnosed in 2018 (Bray et al., 2018). Although most cancer research is mainly focused on tackling molecular and cellular pathways (microenvironment), there is now clear evidence that interactions of an individual with their physical and social environment (macroenvironment) can influence disease progression (McEwen, 2012; Borgi et al., 2020). Stressful conditions, in particular, are a recognized risk factor for cancer in the clinic and are linked to breast cancer aggressiveness in animal models (Hermes et al., 2009; Volden et al., 2013). Animal studies of breast cancer consistently show that exposure to stress potentiates tumor growth and metastasis (Hermes et al., 2009; Williams et al., 2009; Madden et al., 2013; Volden et al., 2013).

Stress response begins in the brain with the perception and elaboration of external challenges and affects the brain as well as the rest of the body through plastic changes, leading to adaptation. The connection between central stress responses and peripheral target organs triggers a cascade of events involving the activation of a number of neurochemical and inflammatory mediators, such as cytokines, chemokines, and growth factors, modifying cell function/survival, metabolism and behavior, in order to best deal with a stressful challenge (Hayley et al., 2005; Cirulli and Alleva, 2009; Capoccia et al., 2013). Indeed, the stress response involves the activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, increasing the secretion of catecholamines and glucocorticoids (GCs), respectively. While the coordinated activation of the stress machinery is pivotal in the short run (acute conditions) to cope with external threats yet, over longer time intervals (chronic stress), it imposes a cost, rendering the organism more vulnerable to pathological conditions (McEwen, 2007). Indeed, chronic stress has been associated to the onset/precipitation of psychiatric disorders and to altered immune responses possibly affecting neoplastic progression both in humans and animal models (Cavigelli et al., 2008). In particular, it is thought to dysregulate immune function through (i) the suppression of protective immunity, (ii) the enhancement of immunosuppressive mechanisms and (iii) the induction/exacerbation of chronic inflammation (Dhabhar, 2009, 2014, 2018; Antoni and Dhabhar, 2019; Zhang et al., 2020).

Cao et al. (2010) in a very intriguing study, provided evidence that environmental/social enrichment is able to reduce tumor growth and increase remission in mouse models of melanoma and colon cancer. Mice exposed to an enriched environment were characterized by increased hypothalamic Brain-Derived Neurotrophic Factor (*Bdnf*) levels associated to decreased leptin and increased adiponectin production in the white adipose tissue (WAT) (Cao et al., 2010; Cao and During, 2012; Liu et al., 2014). Mammary fat is the most abundant component of the breast and is the most probable candidate to affect tumor behavior because adipocytes produce hormones, growth factors, and adipokines. There is increasing evidence that adipokines, such as adiponectin and leptin, secreted by peri-tumoral adipose tissue are involved in several tumors, such as breast cancer (Miyoshi et al., 2006; Schäffler et al., 2007). Adipokines are a heterogeneous class of molecules produced prevalently by WAT that have emerged as modulators of inflammation and immune responses. In addition, they also act as messengers to communicate to the brain the peripheral metabolic status (Schäffler et al., 2007).

Moreover, and most intriguingly, adipokines are emerging as depression biomarkers, and changes in their circulating levels have been related to the severity of depressive symptoms, particularly in young women (Carvalho et al., 2014; Everson-Rose et al., 2018; Syk et al., 2019). Indeed, depressive symptoms often accompany patients with breast cancer as a result of situational fear related to diagnosis and prognosis (Raison and Miller, 2003). In this regard, it is worth noticing that the tumor itself can produce depressive symptoms by triggering systemic inflammatory responses generating a positive feedback loop between coping style and cancer progression (Sephton et al., 2009). Such mechanisms may be greatly affected by environmental conditions, with stressful events overall decreasing the ability to cope with cancer.

While an enriched environment was shown to reduce tumor growth and increase remission (Cao et al., 2010), in animal models of cancer, we have previously shown that social isolation leads to reduced BDNF levels, and increased anxiety and depressive-like behaviors, accompanied by higher levels of corticosterone, all conditions that might favor cancer progression (Berry et al., 2012). BDNF is a neurotrophin highly expressed in the hippocampus and in the hypothalamus, whose levels are decreased as a result of excessive exposure to GCs (Tapia-Arancibia et al., 2004; Price et al., 2018). It plays a key role in neuronal plasticity and the modulation of emotionality as well as in the integration of neuroendocrine and metabolic pathways in response to stressful challenges (Cirulli and Alleva, 2009). Indeed, social isolation, which is commonly experienced by patients with cancer, may represent a critical condition exacerbating depressive symptoms and promoting tumor activity (Pantell et al., 2013; Sumis et al., 2016). People who experience

isolation stress (IS) show a worse prognosis and present an elevated chance to die from cancer, such as breast cancer, compared with individuals with a richer social life (Berkman et al., 2004; Kroenke et al., 2006). Worth noticing is that while research on the effects of different stressors on breast cancer growth has, so far, resulted in conflicting evidence (both human and animal studies), IS has been shown to consistently elevate cancer risk and mortality (Hilakivi-Clarke et al., 1994; Sumis et al., 2016). In this regard, it has been recently suggested that socially isolated individuals may be characterized by a unique physiological *milieu* able to promote tumor growth (Hinzey et al., 2016). Thus, the aim of this study was to characterize the effects of four-month chronic social IS on tumor progression in female subjects of the MMTVNeuTg strain, a mouse model of brest cancer susceptibility. These mice overexpress the ErbB2 receptor, a condition observed in advanced breast cancers with an especially poor clinical prognosis (Slamon et al., 1987; Perou et al., 2000; Ursini-Siegel et al., 2007) thus, this model was selected because of its late latency of tumor occurrence, which allows studying the effects of chronic IS. We hypothesized that IS may activate the neuroendocrine and sympathetic nervous systems, leading to main changes in the hypothalamic expression levels of *Bdnf* and other stress-responsive mediators regulating mood and metabolism, such as Neuropeptide Y (*NpY*), Agouti-Related Peptide (*AgRP*), and Serum/Glucocorticoid-Regulated Protein Kinase 1 (Anacker et al., 2013; Baver et al., 2014). We focused on the hypothalamus, a brain area critical in the regulation of both energy balance and neuroendocrine activation. We also hypothesized that such stress-driven changes in the brain may, in turn, affect the production of mammary fat pad-derived adipokines and lead to depressive symptoms, eventually enhancing tumor progression. In this regard, mice were also scored for the occurrence of depressive-like behaviors by means of a saccharin preference and a forced swimming test (Berry et al., 2012). Neuroendocrine activation might greatly affect energy balance and promote fat browning (Razzoli and Bartolomucci, 2016; Razzoli et al., 2016). Indeed, metabolic reprogramming is a hallmark of cancer, and a growing body of evidence suggests that fat browning may be associated to a worst prognosis of different types of cancer (Hanahan and Weinberg, 2011; Huang et al., 2018). We also set to analyze the presence of fat browning as a marker of worst prognosis in the mammary fat pads of the MMTVNeuTg mice.

MATERIALS AND METHODS

Animals

The experimental subjects were ErbB-2(Neu)TgMMTV-ErbB-2 (FVB background) mice purchased from The Jackson Laboratory (Bar Harbor, ME, United States) *via* Charles River (Calco, Italy). Upon arrival, all the animals were housed in the same room and provided with air conditioning (temperature 21 ± 1°C, relative humidity 60 ± 10%), in transparent Plexiglas cages (29 × 12 × 14 cm), under a reversed 12/12 h light/dark cycle with lights off from 0800 to 2000 h. Pellet food (standard diet Altromin-R, Rieper, Italy) and tap water were continuously available. More in detail, the MMTVNeuTg subjects developed hyperplasia at 5 months and focal adenocarcinoma and lung metastases at 7 months. The mice were used to fulfill the criteria of: (i) late latency of tumor occurrence to allow chronic stress treatment and (ii) extensively characterized tumor model with respect to morphological and histological features. The subjects in this experiment were 35 MMTVNeuTg female mice. At weaning, 16 of them were socially isolated (isolation stress, IS) to model long-term stress and, 19 were housed under standard laboratory conditions (group housing, GH−2 to 3 subjects/cage). Once a week, from the age of 16 weeks until week 20, each mouse was inspected for the presence of breast lumps. At this time point, approximately half of the subjects from each housing condition group were subjected to acute restraint stress (RS) to assess the functionality of the HPA axis ($n = 10$ MMTVNeuTg group-housed RS; $n = 8$ MMTVNeuTg isolated RS; see below for further details on the procedure). All the other subjects ($n = 9$ MMTVNeuTg group-housed control; $n = 8$ MMTVNeuTg isolated control) were assessed for depressive-like behavior by scoring the anhedonic profile (saccharin preference test) and learned helplessness (forced swimming test). At the end of the procedures, all the subjects were sacrificed to collect central and peripheral tissues in order to assess CORT levels (blood) and the gene expression of *Bdnf*, *SgK1*, *AgRP* and *NpY* (hypothalamus) as well as leptin and adiponectin and fat browning (in mammary gland fat pads) (see **Figure 1**).

All experimental procedures were reviewed by the ethical body of the Istituto Superiore di Sanità for animal welfare and conducted in conformity with the European Directive 2010/63/EU and the Italian legislation on animal experimentation, D.Lgs. 26/2014. They were authorized by the Italian Ministry of Health.

Experimental Procedures

Restraint Stress

Following 4 months of isolation, half of the animals deriving from both the IS and GH (10 GH mice and 8 IS mice) underwent an acute RS procedure in order to assess the activity of the HPA axis. Each mouse was introduced in a conical 50-ml Falcon tube, provided with holes for breathing, adjusted on a laboratory bench with tape to prevent rolling. The stress was administered once and lasted three consecutive hours. To assess changes in CORT levels, blood samples were collected by tail nick at 0 (basal) 180 from the onset of stress, and after 240 min the mice were removed from the tube and sacrificed to collect trunk blood.

Saccharin Preference: Anhedonia

Mice have a strong preference for sweet solutions, such as those containing sucrose or saccharin, and the intake of these compounds is considered to result from their hedonic properties (Cryan and Holmes, 2005; Branchi et al., 2013). Twenty-week-old mice were habituated to a saccharin solution for 3 days. After this period, the experimental subjects underwent 10 days of familiarization, and each cage was provided with two bottles, one containing fresh tap-water and one containing 0.1% of saccharin solution. Bottles were daily weighed in order to monitor liquid consumption and switched to balance the effect of side preference in drinking behavior, which has been reported

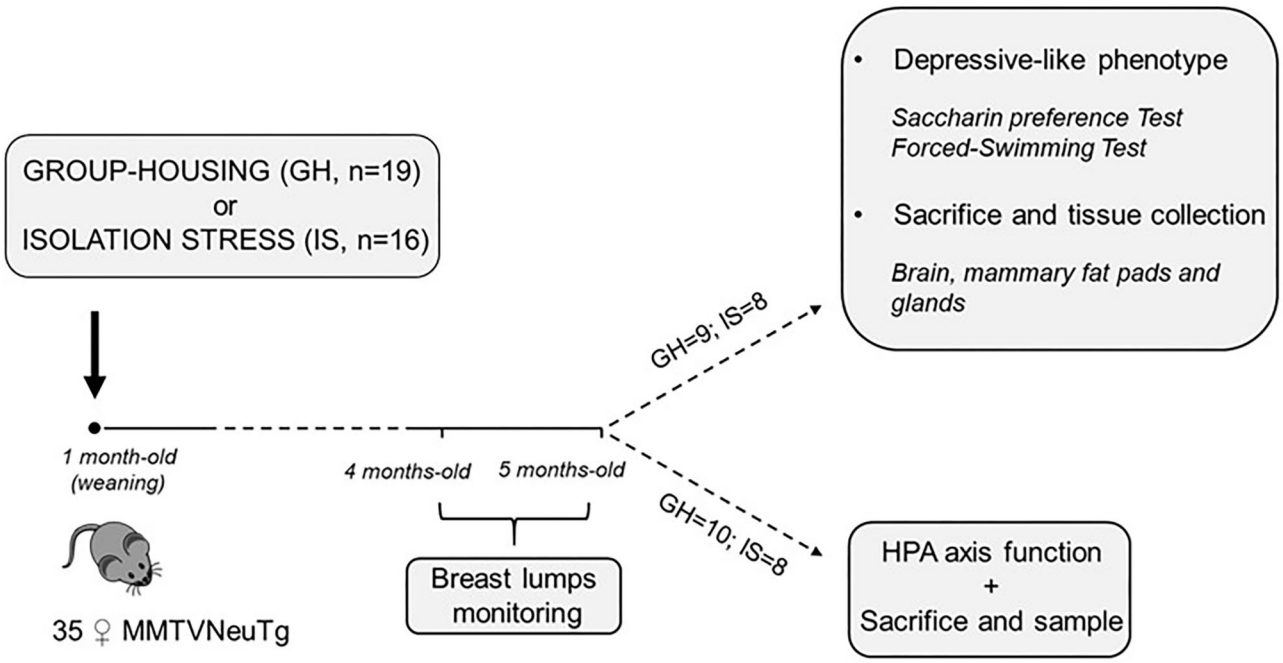

FIGURE 1 | Timeline of the experimental design.

to be of importance for the correct evaluation of saccharin preference (Strekalova et al., 2004; Branchi et al., 2013).

Saccharin consumption was derived from bottle weight, and preference was evaluated on day 10 by looking at single mouse consumption for IS, while average cage-consumption was considered for GH. Saccharin preference was then calculated as follows:

$$\%\text{saccharin preference} = \frac{\text{Saccharin solution intake} \times 100}{\text{water intake} + \text{Saccharin solution intake}}$$

Forced Swimming Test: Learned Helplessness

The mice were tested according to the procedure developed by Porsolt et al. (1977). Each experimental subject was gently placed into a cylindrical glass (20 cm Ø, 40 cm height), filled with 25 cm of water at a temperature of 26 ± 1°C for 6 min for two consecutive days with dim light illumination (1 lux). When removed from the water, the mice were allowed to dry for 5 min under red light. Twenty-four hours later, a second session took place and latency, frequency, and duration of the following behavioral responses were scored: struggling (vigorous attempts at climbing the walls of the cylinder), swimming (active swimming around) and floating (total absence of movement).

Radioimmunoassay for Corticosterone Determination

Blood samples (20 μl, approximate volume) were collected individually in potassium EDTA coated tubes (1.6 mg EDTA/ml blood, Sarstedt, Germany). All samples were kept on ice and later centrifuged at 3,000 rpm for 15 min at +4°C. Blood plasma was transferred to Eppendorf tubes for CORT determination and stored at −20°C until further analysis. CORT was measured using a commercially available radioimmunoassay (RIA) kit containing 125 iodine labeled CORT; 5 μl of plasma was sufficient to carry out the CORT measurement. Sensitivity of the assay was 0.125 mg/dl, inter- and intra-assay variation was <10 and 5%, respectively (MP Biomedicals Inc., Santa Ana, CA, United States). Vials were counted for 2 min in a gamma-scintillation counter (Packard Minaxi Gamma counter, Series 5000).

Quantitative Real-Time Reverse Transcription–PCR

Total RNA was extracted from frozen hypothalamic and subcutaneous white adipose tissues with Trizol (Invitrogen, Carlsbad, CA, United States) and RNeasy Lipid Tissue Mini Kit (Qiagen, Hilden, Germany) following the instructions of the manufacturer. Quantity and quality were assessed with a Nanodrop ND-1000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA) using OD260 for calculation of the concentration and the ratios 260/280 and 260/230 for assessing the purity of the samples. After cDNA synthesis using Superscript III (Invitrogen, Carlsbad, CA, United States), Real-time RT-PCR was performed with the TaqMan technology, using the ABI PRISM 7700 DNA Sequence Detection System (Applied Biosystems, Foster City, CA, United States). TaqMan reactions were carried out in 96-well plates using cDNA, TaqMan universal PCR mastermix, preoptimized, and preformulated TaqMan gene expressions assays that included specific primers and fluorescent probes for mouse, and water to a final volume of 25 μl according to the instructions of the manufacturer. Commercial ready-to-use primers/probe mixes

(Assays on Demand Products, Applied Biosystems, Waltham, MA, United States) are listed: Adipoq #Mm00456425_m1; Lep #Mm00434759_m1; Insr #Mm01211875_m1; Bdnf # Mm 04230607_s1; Sgk1 #Mm 00441387_g1; Agrp #Mm 00475829_g1; Lepr #Mm 00440181_m1, Npy #Mm 03048253_m1; Eef2 #Mm 01171435_gh; GAPDH #Mm99999915_g1. Eef2 and GAPDH genes were used as internal controls for the efficiency of the RT-PCR assay and for the subsequent normalization of gene expression as assessed in the hypothalamus as well as in the adipose tissue, respectively. The Δct values were used for statistical analysis.

Assessment of Breast Lumps

The effects of prolonged social isolation (4 months) on the onset of breast lumps were assessed on female mice that were socially isolated from weaning until 5 months of age. Briefly, after a week from the arrival in the animal facility, the mice were either group housed (2–3 subjects/cage) or singly housed in cages with the following dimensions (29 × 12 × 14 cm). Once a week from the age of 16 weeks until week 20, each mouse was inspected for the presence of breast lumps through palpation of the 10 mammary glands. The inspection was carried out by trained personnel. The procedure for mammary gland monitoring and breast lumps detection in the MMTVNeuTg mice was adopted by other studies on ErbB2 transgenic mice with similar spontaneous carcinogenesis timing performed by the group of the authors or others (Boggio et al., 1998; Castiello et al., 2018). In particular, in order to limit operator-related biases, a very experienced technician took the responsibility of performing the procedure throughout the study duration.

Histology: Fat Browning and Proliferation Analysis

Hematoxylin and eosin staining (H&E) was performed on formalin fixed paraffin embedded (FFPE) tissue sections from the 5-month-old subjects ($n = 5$ for each experimental group). Slides (5 μm thick) were deparaffinized and hydrated through graded alcohols, and the H&E staining was performed according to standard protocols.

For immunolocalization studies, serial sections from two-mice-group of breast tissue were subjected to antigenic retrieval in Tris-EDTA pH 9 buffer, permeabilizated in 0.1% Triton X-100, saturated in 3% bovine serum albumin (BSA) at room temperature, and incubated with the rabbit anti- Ki-67 antibody (IHC-00375, Bethyl Laboratories, Inc. Montgomery, TX, United States) and subsequently with Alexa Fluor 555 conjugated anti-rabbit antibody (Molecular Probes, Eugene, OR, United States). Nuclei were stained with Hoechst 33342 (H3570, Invitrogen, Carlsbad, CA, United States). Negative controls were performed by omission of the primary antibody. Finally, the slides mounted with ProLong Gold Antifade (P36930, Invitrogen, Carlsbad, CA, United States) were analyzed by Olympus F1000 laser-scanning confocal microscopy (Olympus, Tokyo, Japan) (Maselli et al., 2019).

Statistical Analysis

Data were analyzed using parametric analysis of variance (ANOVA) with "social condition" (group-housed and isolation stress) as between-subjects factor and "time course" as within-subject repeated measures (CORT assessment; breast lumps). For outcomes that did not follow a normal distribution (*Bdnf*, *NpY*, *SgK1* and *AgRP*) data were normalized by transforming raw data into their square root. *Post-hoc* comparisons were performed using the Tukey's test. Statistical analysis was performed using Statview II (Abacus Concepts, Berkeley, CA, United States). Data are presented graphically as means ± SEM and as box plot (observations outside the ranges are represented with dots outside the boxes). A significance level of 0.05 was chosen.

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

RESULTS

HPA Axis Assessment

When the mice were challenged with an acute RS to assess neuroendocrine reactivity following a chronic IS procedure, a main effect of the social conditions was observed, showing overall increased CORT levels in the IS group [$F_{(1,16)} = 11.223$; $p = 0.0041$]. More in detail, while basal levels did not differ between IS and GH mice, a significant interaction between social condition and time course revealed that IS resulted in a specific increase in CORT levels both at 180 and 240 min from the beginning of the RS procedures $F_{(2,32)} = 4.394$; $P = 0.0206$ (*post-hoc* comparison $P < 0.05$, see **Figure 2**).

Saccharin Preference: Anhedonia

When the hedonic profile of female mice that experienced 4 months of social isolation was characterized, we observed an elevated preference toward saccharin consumption in the IS group when compared with the GH condition [$F_{(1,9)} = 7.844$; $p = 0.0207$], confirming that prolonged social isolation influences response to stimuli associated with reward as previously shown (Berry et al., 2012).

Forced Swimming Test—Learned Helplessness

Assessment of the learned helplessness profile, as a result of IS, showed that the female mice, isolated for 4 months, were characterized by a specific decrease in the frequency and duration of struggling, an escape-like behavior indicative of a proactive coping strategy toward stress [$F_{(1,15)} = 9.022$; $p = 0.0089$; $F_{(1,15)} = 10.204$; $p = 0.0060$, respectively for frequency and duration]; latency to display this behavior did not differ between IS and GH [$F_{(1,15)} = 1.072$; $p = 0.3169$]. Swimming behavior was also affected by IS, since these mice showed a decreased number of swimming bouts [frequency: $F_{(1,15)} = 5.093$; $p = 0.0394$)]. However, latency and duration were not affected by chronic stress [$F_{(1,15)} = 0.821$; $p = 0.3792$; $F_{(1,15)} = 3.371$; $p = 0.0863$]. The IS and GH mice did not differ as for floating behavior [$F_{(1,15)} = 0.132$; 0.247; 1.032; $p = 0.7212$; 0.6267; 0.3258, respectively, for latency, frequency, and duration; see **Figure 2**].

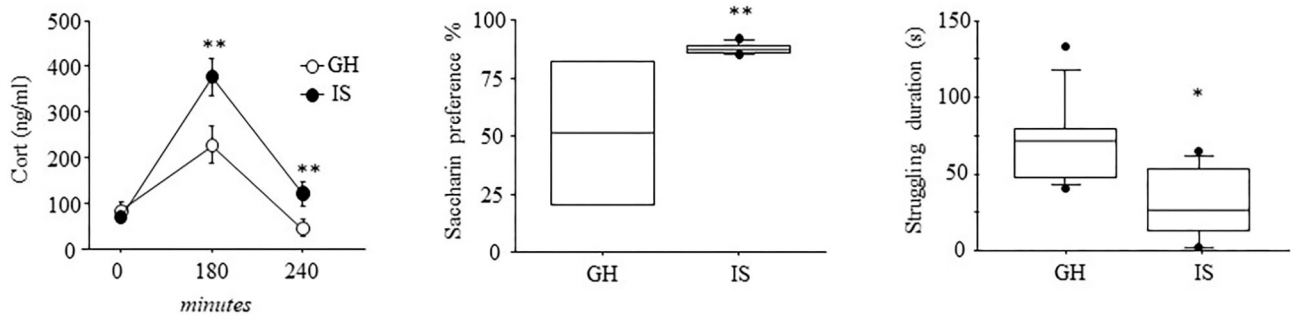

FIGURE 2 | Neuroendocrine and depressive-like behavioral profile of the MMTVNeuTg mice. Three hours of acute restraint stress resulted in higher CORT levels in the MMTVNeuTg female mice that underwent 4 months of chronic isolation stress, suggesting a stronger activation of the neuroendocrine system. The isolated mice were also characterized by elevated saccharin consumption in a saccharin preference test, as well as by reduced struggling duration, suggesting a depressive-like behavior. Data are presented graphically as means ± SEM box plots (observations outside the ranges are represented with dots outside the boxes). $^{*}p < 0.05$; $^{**}p < 0.01$. Number of subjects for CORT: 8 (IS); 10 (GH); for saccharin preference: IS (7) and GH (4); for forced swim stress IS (8); GH (9).

Hypothalamic Gene Expression in Response to Stress

At 5 months of age, a time when tumor progression manifests in the MMTVNeuTg mice, *Bdnf* levels did not differ between the IS and GH subjects [$F_{(1,8)} = 3.698$; $P = 0.907$]. In contrast, the IS mice were characterized by decreased levels of *NpY* [$F_{(1,8)} = 23.784$; $P = 0.0012$], *SgK1* [$F_{(1,7)} = 22.893$; $P = 0.002$] and *AgRP* [$F_{(1,8)} = 39.056$; $P = 0.0002$]; see **Figure 3**.

Gene Expression in Adipose Tissue

At 5 months of age, IS increased both the *leptin* and *adiponectin* gene expressions in the mammary fat pads [$F_{(1,8)} = 9.768$; $P = 0.0141$; $F_{(1,8)} = 52.326$; $P < 0.0001$, respectively, for leptin and adiponectin]; see **Figure 4**.

Assessment of Breast Lumps

Twenty weeks of social isolation resulted in a greater number of breast lumps compared with group-housed controls [main effect of the social condition: $F_{(1,33)} = 8.325$; $p = 0.0068$]. This effect was particularly apparent starting from weeks 18 to 20 [interaction between housing condition and time course: $F_{(4,132)} = 6.696$; $p < 0.0001$; *post-hoc* comparisons $p < 0.01$ IS v. GH at weeks 18, 19, and 20; see **Figure 5**]. To exclude the effects of hormonal fluctuations on breast lump appearance, the subjects were inspected to assess estral cycle phase just before the beginning of RS, and no difference was observed in vaginal smear between the groups (data not shown).

Qualitative Analyses on Breast Tissues

Histological examination of the mammary glands indicated that prolonged exposure to chronic IS induced WAT "browning" in the mammary fat pads with adipocytes being characterized by multilocular small lipid drops. In contrast, the WAT tissue of the GH mice was characterized by cells with a single (unilocular) large lipid drop (**Figure 5**, lower panel, A and B). Moreover, when compared with GH, analysis by confocal microscopy revealed that the IS mice were characterized by greater Ki-67+ cells (red nuclei), suggesting greater cellular proliferation (**Figure 5**, lower panel, C and D).

DISCUSSION

The main aim of this study was to characterize the effects of chronic social isolation stress (IS)—started soon after weaning—on the crosstalk between brain and mammary fat pads in a mouse model of breast cancer. The results show that IS increases neuroendocrine responsiveness to further stressors and lead to important changes in the hedonic profile (saccharin preference test) and copying strategies (forced swimming test); this behavioral phenotype is accompanied by a strong downregulation of hypothalamic genes involved in stress and metabolic regulations, such as *NpY*, *AgRP* and *SgK1*. Moreover, and most importantly, the mammary fat pads of the IS mice show elevated adipokines expression levels and an increased amount of BAT. These changes were associated to an earlier appearance of breast lumps in our MMTVNeuTg breast cancer model.

Chronic social isolation did not affect basal CORT levels but resulted in increased HPA axis activation following an acute restraint stress challenge. These changes in the neuroendocrine response were accompanied by a depression-like phenotype. Indeed, the IS mice showed increased saccharin consumption, in addition to a decrease in the frequency and duration of struggling and in the duration of swimming behavior, as assessed in the forced swimming test. These results are in agreement with the previous data showing that 3 weeks of IS, in male mice, lead to HPA axis hyper-responsiveness to acute challenges, and this was associated to an increase in the consumption of a sweetened solution (Berry et al., 2012). Anhedonia is a core symptom of depression relying upon a reduced ability to feel pleasure from everyday life experiences (Rizvi et al., 2016). A very common method to measure anhedonia in laboratory rodents is by assessing the preference for the consumption of sweetened solutions. However, this measure is tricky, and the significance of the stress-induced preference for saccharin is debated, being highly dependent on the type of stress (physical vs. emotional) as

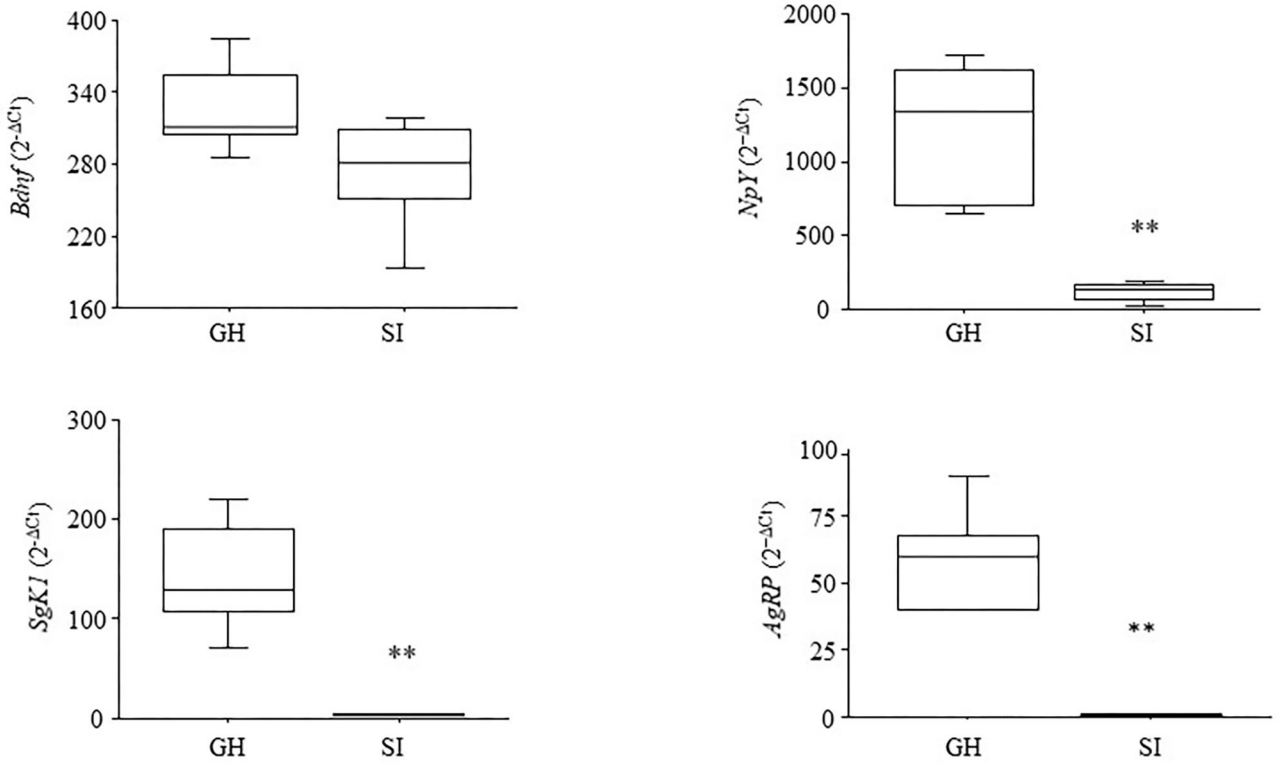

FIGURE 3 | Hypothalamic gene expression. Chronic social isolation stress resulted in the decrease in the expression levels of genes specifically involved in stress reactivity (*SgK1*), and metabolism (*NpY* and *AgRP*). Expression of the neurotrophin *Bdnf* was somewhat reduced but not significantly after 4 months of IS. Raw data were transformed using the square root and are presented graphically as means ± SEM box plots (observations outside the ranges are represented with dots outside the boxes). $^{**}p < 0.01$. Number of subjects: 4–5 within each experimental group.

well as by the metabolic set point of the animals (Adam and Epel, 2007). Worth to notice, Ulrich-Lay et al. provided evidence that saccharin consumption may reduce neuroendocrine activation, suggesting that the rewarding properties of saccharin sweet taste lead to a stress-buffering effect (Ulrich-Lai et al., 2010). Thus, the increase in saccharin preference that we observed in this and the previous study might represent a coping strategy to dampen the stress resulting from the chronic IS condition (Berry et al., 2012). In the forced swimming test, the IS mice showed a decrease in struggling and swimming behaviors, a condition clearly mirroring the shift from an active to a more passive coping strategy, overall suggesting the expression of a depressive-like behavior. Although we did not observe differences in floating between the IS and the GH mice, we cannot exclude that by re-exposing the animals to a second session (like in the standard paradigm of this test) we could have also observed an increase in this behavior.

Stress begins with the perception and interpretation of everyday challenges, leading to plastic changes in the brain and peripheral functions that may affect disease onset/progression (McEwen, 2012; Borgi et al., 2020). The hypothalamus is the brain region capable of integrating different inputs from the external environment, thus the analysis was focused on hypothalamic genes previously shown by Cao et al. to be activated in animal models of cancer following environmental enrichment. Interestingly, and as hypothesized, we found decreased levels of those same genes found to be activated upon social/environmental enrichment by these authors (Cao et al., 2010). More in detail, while we found a specific decrease in *SgK1*, *AgRP*, and *NpY*, no change was observed upon *Bdnf* assessment. This neurotrophin is highly expressed in the hypothalamus, and its transcription is complex and shows great variation across different nuclei (Timmusk et al., 1993; Chen et al., 2003; Miranda et al., 2019). However, we measured BDNF expression levels in the whole hypothalamus, and this might have reduced the chance to appreciate significant differences.

Levels of *SgK1* were decreased in the hypothalamus of our mouse model of breast cancer when subjected to IS. This gene is involved in many important GC-dependent functions affecting both stress and metabolism (Ullrich et al., 2005; Van Gemert et al., 2006; Anacker et al., 2013; Deng et al., 2018). Decreased *SgK1* in the prefrontal cortex has been associated to stress-related behavioral and morphological phenotypes in both human and animal studies (Licznerski et al., 2015). Moreover, decreased

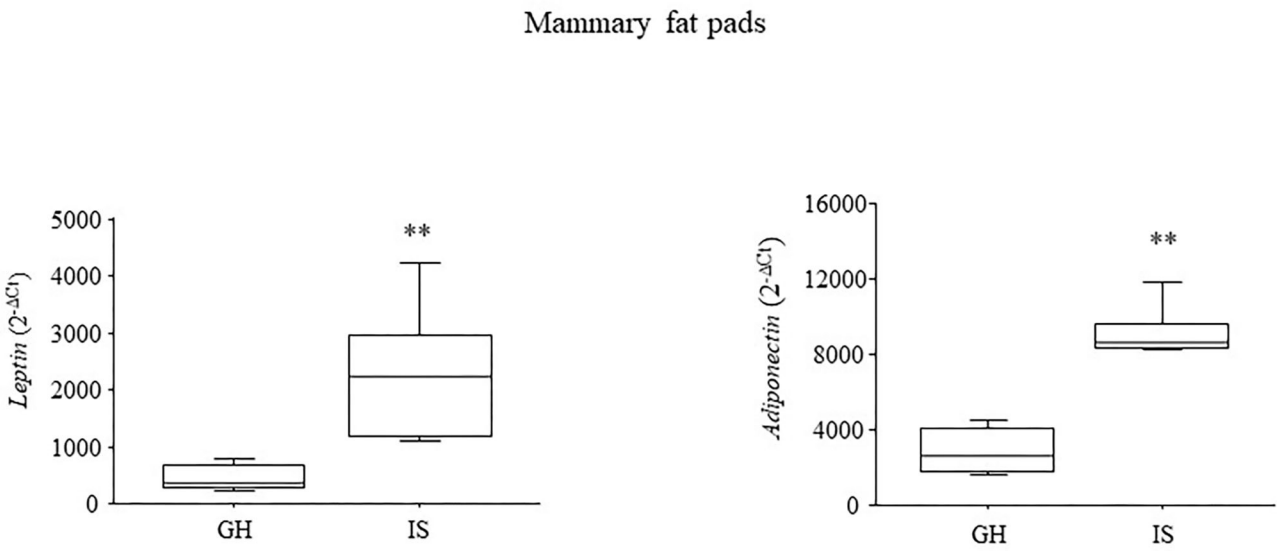

FIGURE 4 | Adipokines gene expression in the mammary fat pads. Chronic social isolation stress increased the levels of leptin and adiponectin in the MMTVNeuTg female mice. Data are presented graphically as means ± SEM box plots (observations outside the ranges are represented with dots outside the boxes). $^{**}p < 0.01$. Number of subjects: 4–5 within each experimental group.

hypothalamic levels of *SgK1* were observed upon dexamethasone infusion (a selective GR agonist) and were associated to increased adiposity without changes in body weight, suggesting that this molecule may represent a link between emotional distress and fat metabolism (Deng et al., 2018).

AgRP and *NpY* are powerful orexigenic neuropeptides that play a main role in energy homeostasis; within the central nervous system they are expressed primarily in the hypothalamus and are (down-) regulated by peripheral nutritional factors that include fat-secreted leptin (Mizuno et al., 2003). Recently a role for *AgRP* has been proposed in the orchestration of the complex interaction among stress, food reward and ingestive behavior (Fang et al., 2021) such that when *AgRP* neuronal activity is impaired, neural circuits sensitive to emotion and stress (pro-opiomelanocortin—POMC) are engaged and finely modulate food palatability (Denis et al., 2015; Morales and Berridge, 2020). Indeed, our data show that the IS mice were characterized by reduced hypothalamic *AgRP* expression levels and increased consumption of saccharin. This piece of data suggests that chronic IS may change individual incentive-sensitization in favor of palatable food rewards (Denis et al., 2015; Morales and Berridge, 2020; Fang et al., 2021). Another important player in these regulations is *NpY*, which, beyond its main role in the control of metabolism and food intake, is also involved in stress coping strategies and in the pathophysiology of depression. Indeed, clinical studies show that increased plasma NPY levels correlate with improved coping abilities (Morgan et al., 2000; Kautz et al., 2017). In contrast, in pathological conditions, such as depression, NPY release is reduced (Redrobe et al., 2002). Animal studies confirm and strengthen the above-mentioned evidence showing, for example, that exposure to chronic variable stress reduces NPY levels within the amygdala (McGuire et al., 2011), while animals being characterized by more adaptive coping strategies show higher *NpY* levels in different brain areas (Hawley et al., 2010). Moreover, intracerebroventricular administration of *NpY* in rats significantly reduces immobility time in the forced swimming test in a dose dependent fashion (Redrobe et al., 2002). This piece of data is particularly interesting, since we observed a reduction in struggling and swimming in the forced swimming test in association with reduced hypothalamic *NpY*, suggesting that this neuropeptide might, at least in part, account for the passive coping strategy observed in this test.

Chronic activation of the stress machinery leads to an allostatic load powerfully affecting both the central nervous system and peripheral organs and tissues; thus, pathological changes in mood and emotionality are often associated to changes in fat metabolism and body weight. We found that the fat pads of the IS mice were characterized by increased leptin and adiponectin expression levels, an effect associated to increased BAT and to an overall earlier appearance of breast lumps, in the absence of significant changes in body weight (data not shown). The data are in line with the findings of Sun et al. who found increased circulating leptin levels and overall increased adiposity (with regard to both WAT and BAT) in IS mice (Sun et al., 2014). Likewise, Volden et al. (2013) found a specific upregulation of leptin levels in the mammary fat pads of a mouse model of breast cancer subjected to IS. The mammary gland is a dynamic organ, mainly composed of fat tissue, that changes its architecture and function in response to hormonal and neuroendocrine triggers. Elevated leptin levels have been observed in macrophage-infiltrated WAT characterized by inflammation and hypertrophy of the adipocytes (Armani et al., 2017). This pro-inflammatory condition is usually associated to decreased adiponectin levels, an anti-inflammatory adipokine, whose blood levels are inversely

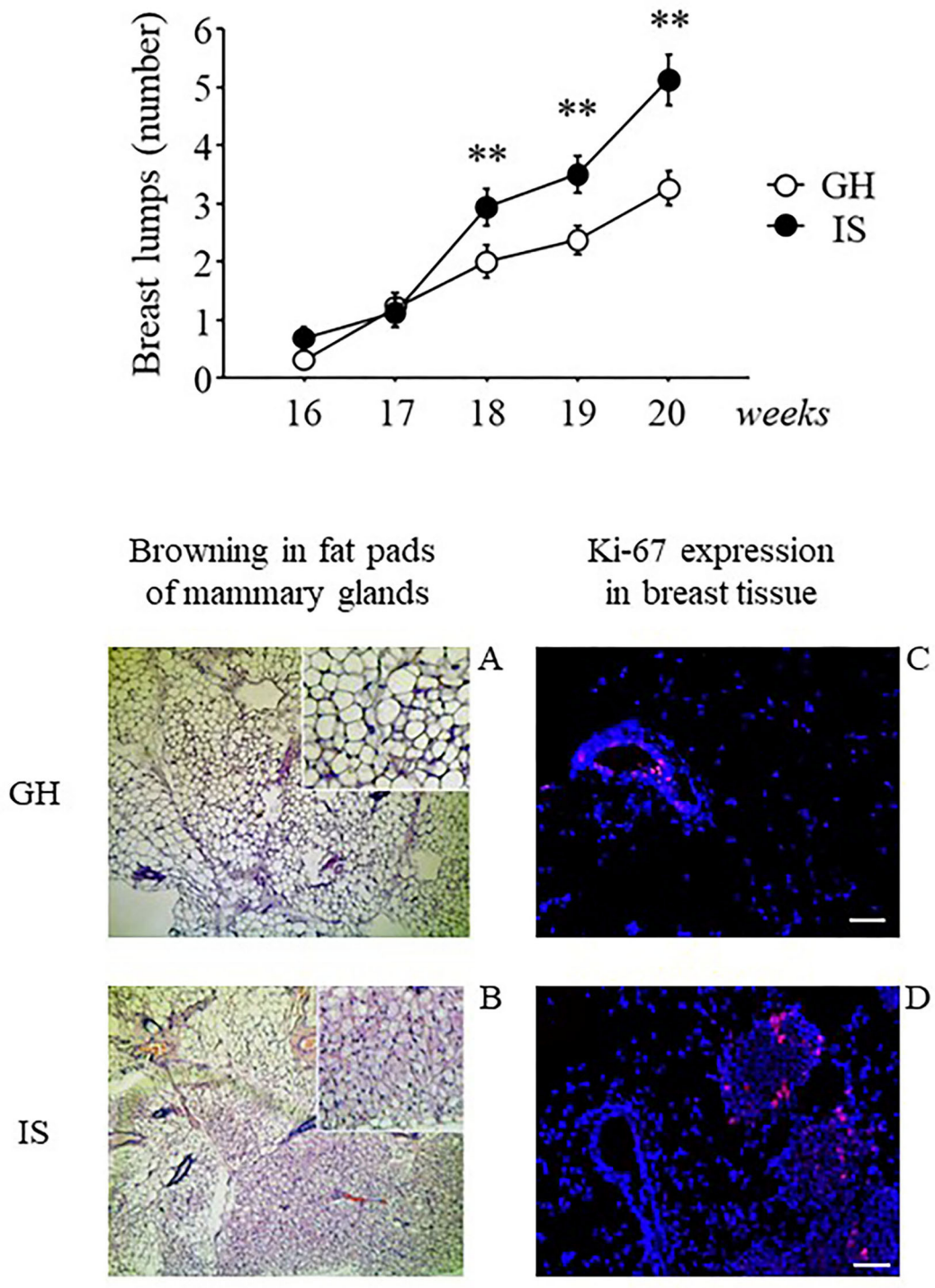

FIGURE 5 | Breast lumps and histological analysis of breast tissues from the MMTVNeuTg female mice. Breast lumps and fat browning in the fat pads of the MMTVNeuTg female mice. Isolation stress resulted in a time-dependent increase in the number of breast lumps in the breast cancer susceptibility MMTVNeuTg mouse model, suggesting an acceleration in tumor onset (upper panel). Moreover, when compared with the GH condition (lower panel, **A** and **C**) chronic IS promoted the development of brown adipose tissue and was associated with a greater number of Ki-67+ cells (red nuclei) in the mammary gland (lower panel, **B** and **D**). Data are presented graphically as means ± SEM (upper panel). *Post-hoc* comparisons: $^{**}p < 0.01$. Number of subjects: IS (16); GH (19). Lower panel: representative sections from mammary fat pads (**A** and **B**) and mammary gland (**C** and **D**), immunostained with Ki-67 (red) and counterstained with Hoechst (blue). Scale bar = 50 μm.

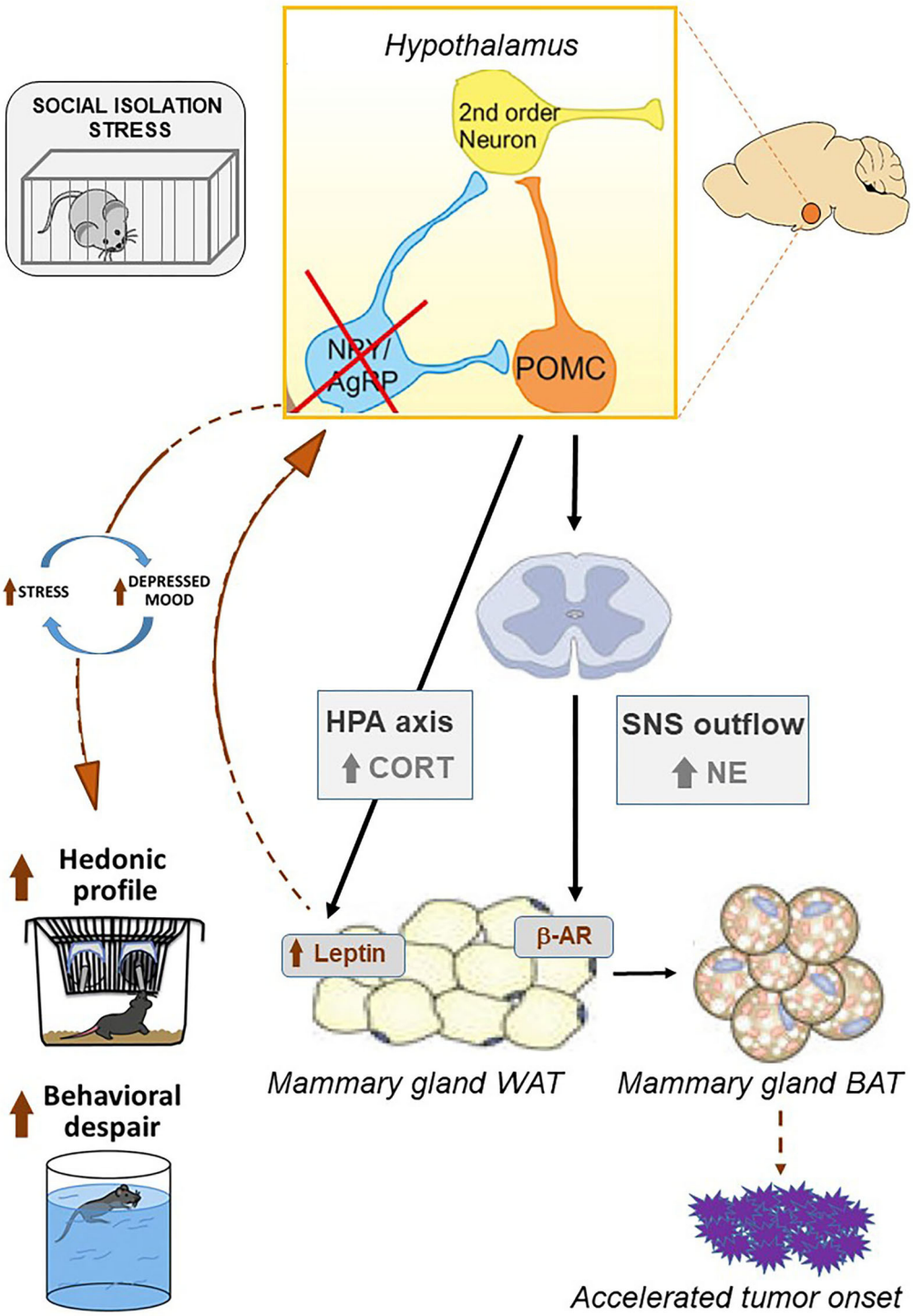

FIGURE 6 | Chronic social isolation stress results in the activation of the hypothalamic-pituitary-adrenal axis. Upon the activation of the HPA axis, corticosterone acts directly on the white adipose tissue by increasing leptin levels. This pro-inflammatory adipokine reaches target neurons in the hypothalamus, resulting in the inhibition of *NpY/AgRP* signaling that in turn increases the neuronal activity of POMC (Baver et al., 2014; Denis et al., 2015; Fang et al., 2021). As a result, an increase in reward-driven saccharin consumption is observed as well as passive coping strategies in the forced swimming test. The appearance of depressive-like behaviors promotes a feed-forward loop promoting chronic stress. Likewise, hypothalamic signaling *via* POMC neurons triggers the activation of the sympathetic nervous system that, by secreting norepinephrine, reaches beta-adrenergic receptors within WAT, promoting the development of brown adipose tissue (Dodd et al., 2015; Caron et al., 2018). BAT is characterized by increased metabolic rate and may, in turn, accelerate tumor onset in the MMTVNeuTg mouse model. Picture modified from Caron et al. (2018), Denis et al. (2015), and Franklin et al. (2012).

related to breast cancer risk in patients (Yu et al., 2019). Here, we found increased levels of adiponectin in the WAT of the IS mice, possibly suggesting a compensatory mechanism in the attempt to restore metabolic homeostasis in the cancer-prone model.

The same studies previously mentioned (Sun et al., 2014) also found important changes in BAT following isolation stress, a result that we also report. This fat tissue is characterized by small numerous adipocytes and a large number of well-developed mitochondria that facilitate the catabolism of lipids for heat production (Carpentier et al., 2018). Wang et al. found that the browning of mammary fat, in the proximity of malignant breast tumors, was greater than that close to benign lesions in a cohort of Chinese women (Wang et al., 2014). Thus, although the mice were sacrificed before the appearance of tumor masses, and we are well aware that breast lumps may not be directly associated to malignant lesions (Daly and Puckett, 2020), we can hypothesize that BAT development in the IS mice might stand for a more aggressive pro-tumorigenic micro-environment. In this context, it is worth to notice that BAT appearance, as a result of isolation stress, holds many implications for cancer pathology, since the phenomenon of fat browning has been associated to negative energy balance as observed during cachexia (a syndrome characterized by uncontrolled weight loss, muscle atrophy, fatigue, and weakness) (Caron et al., 2018). There is also evidence to suggests that leptin feedback on POMC neurons may directly promote fat browning through the activation of the sympathetic nervous system (Dodd et al., 2015; Caron et al., 2018). At the same time, the inhibition of *NpY/AgRP* signaling by leptin may drive emotional responses and activate the reward system (in the attempt to buffer stress) through the activation of POMC neurons (Baver et al., 2014; Denis et al., 2015; Fang et al., 2021).

CONCLUSIONS AND FUTURE PERSPECTIVES

This study has some limitation that is mainly linked to the specific animal model, which is a mouse transgene that only partially reproduces the complexity of cancer onset and progression. Furthermore, we were limited in the number of subjects used. Nonetheless, we suggest that these data are important as they point to IS as a pervasive stressor that is able to specifically target and affect neuronal circuits, mastered by the hypothalamus, modulating mood, stress-reactivity, and energy homeostasis. The activation of such IS-driven machinery may hold main implications for the onset and maintenance of pro-tumorigenic environments (see **Figure 6**).

Recent evidence has suggested that the efficacy of existing cancer therapies is impaired by chronic stress, because it prevents the immune system from responding properly (Zhang et al., 2020). Moreover, the metabolic requirements of immune cells in the tumor microenvironment greatly influence the success of immunotherapy such that the use of metabolic modulators has been proposed as a potential strategy to "support energetic rewiring of immune cells that might boost their anti-tumor capacity" (Guerra et al., 2020). Thus, from a translational perspective, beyond primary strategies to counteract social isolation and to promote social support, tailored dietary strategies and lifestyle interventions that should include physical activity (Cui et al., 2019) hold the potential to improve not only individual metabolic set point but also mood, ultimately targeting the stress-immune-cancer axis.

Sex and gender represent primary variables affecting different elements of the stress process, such as how a stressful event is perceived, as well as coping responses. A growing body of research has shown striking sex biases in stress-related anxiety and mood disorders with women more likely than men to develop depression during their lifetime. Thus, a special attention should be given to the appraisal of stressors of women (Borgi et al., 2020).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Ethical Body of the Istituto Superiore di Sanità for Animal Welfare and conducted in conformity with the European Directive 2010/63/EU and the Italian legislation on animal experimentation, D. Lgs. 26/2014. They were authorized by the Italian Ministry of Health.

AUTHOR CONTRIBUTIONS

AB and BC analyzed, interpreted data, and wrote the manuscript. SCa collected all behavioral data. MTD and EA provided their expertise in the mouse model of breast cancer. SCe and PS carried out immunohistochemistry of BAT. CR and EO carried out gene expression. RP and GP carried-out the ki-67 analysis on breast tissue, interpreted data, and drafted the revised version of the manuscript. FC designed the experiment and provided data interpretation. All authors contributed to the article and approved the submitted version.

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Family and Community Support, Brain-Derived Neurotrophic Factor, and Cognitive Performance in Older Adults: Findings From the Health, Wellbeing and Aging Study Population-Based Cohort

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Background: Social networks can modulate physiological responses, protects against the detrimental consequences of prolonged stress, and enhance health outcomes. Family ties represent an essential source of social networks among older adults. However, the impact of family support on cognitive performance and the biological factors influencing that relationship is still unclear. We aimed to determine the relationship between family support, cognitive performance and BDNF levels.

Methods: Cross-sectional data from three-hundred, eight-six individuals aged on average 60 years enrolled in the Health, Wellbeing and Aging Study (SABE), a population-cohort study, were assessed for family support, community support and cognitive performance. Structural and functional family support was evaluated based on family size and interactions allied to scores in the Family APGAR questionnaire. Community assistance (received or provided) assessed the community support. Cognitive performance was determined using the Mini-Mental State Examination (MMSE), verbal fluency (animals per minute) and backward digital span. Blood samples were obtained to determine BDNF levels.

Results: Multivariate analysis showed that functional family support, but not structural, was associated with higher MMSE, verbal fluency and digit span scores, even controlling for potential cofounders ($p < 0.001$). Providing support to the community, rather than receiving support from others, was associated with better cognitive performance ($p < 0.001$). BDNF concentration was not associated with community support, family function, or cognitive performance.

Conclusion: These findings suggest that emotional components of functional family and community support (e.g., loving and empathic relationship) may be more significant to cognitive health than size and frequency of social interactions.

Keywords: social support, family support, cognition, BDNF, aging

INTRODUCTION

Prolonged exposure to stress mediators allied to maladaptive coping strategies is believed to influence the increased variability of cognitive functioning throughout adulthood and aging (Juster et al., 2010). Identifying protective factors capable of counterbalancing the negative impact of stress on the brain is critical to reducing the dementia burden worldwide.

The emerging literature on social support has shown that social networks and relationships modulate physiological responses (Uchino et al., 1996; Bowen and McGregor, 2014), protects against the detrimental consequences of stress (Heinrichs et al., 2003; McQuaid et al., 2016; Costa-Cordella et al., 2021), and enhance mental and physical health outcomes (Havranek et al., 2015; Ginting et al., 2016), through the use of active coping mechanisms when dealing with stressful life situations (Ozbay et al., 2007).

Social support is defined as structural and functional assistance/help that an individual can receive from family, friends, neighbors, and community members in times of need (Costa-Cordella et al., 2021). According to theoretical models of social support, structural assistance refers to the size and frequency of social interactions; while functional is the quality of relationships, which includes emotional (receiving love, encouragement and positive feedback) and instrumental components (provision of financial help, assistance with childcare, caregiving) (Southwick et al., 2005).

Longitudinal studies on the effect of perceived social support on health outcomes show that having significant companionship reduces the risk of heart disease and cardiovascular incidents (Anthony and O'Brien, 1999; Havranek et al., 2015; Ginting et al., 2016), respiratory diseases (Cohen et al., 2015) and strokes (Valtorta et al., 2016). In contrast, low social support has been associated with heightened stress reactivity, exaggerated autonomic and neuroendocrine responses to psychological stressors (Uchino et al., 1996).

In the brain, positive effects of social support on cognitive performance were described in older adults (Kelly et al., 2017; Costa-Cordella et al., 2021). Higher levels of social support have been associated with better cognitive functioning and less cognitive decline (Seeman et al., 2001; Kelly et al., 2017). Global cognition, executive functioning, working memory, episodic memory, attention and processing speed were associated with different components of social support such as social activity, social networks and social relationships (Kelly et al., 2017).

The biopsychological mechanisms underlying the positive relationship between social support and cognitive performance remain unclear. Specifically, qualitative and biological elements that underpin the relationship between social network and cognition is quite limited. For example, family ties represent an essential network source among older adults (Ying et al., 2020). A few studies investigated the impact of family support on cognitive performance with varied results (Windsor et al., 2014; Ge et al., 2017; Ying et al., 2020). Windsor et al. (2014) showed that positive exchanges with family were associated with less decline in perceptual speed, with that association attenuated by adjustment for physical functioning and depressive symptoms (Windsor et al., 2014). Ge et al. (2017) showed that higher strain from spouse and friends allied to higher support from friends, had significant associations with higher executive function (Ge et al., 2017). Evidence about the neurobiology basis explaining those associations is also scarce. Salinas et al. (2017) observed that having someone available to provide emotional support most or all of the time was associated with higher brain-derived neurotrophic factor (BDNF) and lower risk to develop dementia (Salinas et al., 2017). Brain-derived neurotrophic factor is a neuroprotective molecule critical for synaptic plasticity and neuronal repair (Emanueli et al., 2003), which is inducible by lifestyle factors and social enrichment (Neeper et al., 1995; Branchi et al., 2006). Given that, BDNF is a potential factor throughout social relationships impact cognition during aging (Salinas et al., 2017). The association between BDNF and other social support elements was not observed and the relationship with family support remains under investigation.

We aimed to determine the relationship between family support, cognitive performance and BDNF levels. We assessed family and community support in a population-based cohort of Brazilian older adults without dementia medical diagnosis to test the hypothesis that those who report more significant family support (e.g., structural and functional) and community support (e.g., received or provided social assistance to others) have better cognitive performance and higher BDNF levels.

MATERIALS AND METHODS

Study Design, Setting and Participants

The present study used Brazilian data from the Health, Wellbeing and Aging Study (SABE), a multicenter study started in 2000 by the Pan American Health Organization to determine older adults' health and living conditions in seven urban centers of Latin America and the Caribbean (Albala et al., 2005). In Brazil, the SABE study was conducted in Sao Paulo, the most populous city in the country, with the highest absolute number of older people, featured by greater diversity due to immigration and internal migration (Lebrao et al., 2019).

In Sao Paulo, SABE was transformed into a multi-cohort longitudinal study to identify changes in the aging process among different generations. Since 2000, 3,257 Brazilian individuals aged 60 years or older, residing in the urban area of the city of Sao Paulo, distributed in four cohorts (A, B, C, and D), were selected through a probabilistic sampling of households registered on census sectors. Visited households were randomly selected through conglomerate sampling. Institutionalized older adults were not included in the SABE study. The first cohort of participants (cohort A in 2000, n = 2,143) was re-evaluated every five years, when new cohorts of individuals aged 60 to 64 were added (cohort B in 2006, cohort C in 2010, cohort D in 2015). All data was obtained through an in-person survey at the participant's house, conducted by trained interviewers and healthcare personnel. Data was composed of health and living conditions assessment, anthropometric and functional evaluation, caloric expenditure, and blood sampling for biochemical and genetic variables. In 2015, new biochemical

and immunological variables were incorporated, including BDNF. Additional details about sampling and recruitment are available elsewhere (Lebrao et al., 2019).

The present study was based on a secondary cross-sectional analysis of cohort D data (n = 386). Only completed data of family functionality, social support, cognitive performance, and BDNF concentration were considered. Data from participants with dementia diagnosis (family report of medical diagnosis or treatment to dementia, including Parkinson's disease) was excluded.

The study was approved by the Human Research Ethics Committee of the University of Sao Paulo Faculty of Public Health (#COEP/23/10), São Paulo, Brazil. All participants provided informed consent and identifying information of participants has been anonymized.

Measures

Family Support

The number of people who lived with the participants, whether they live alone and stay alone most of the time, was used to assess the structural component of family support (e.g., size and frequency of interactions). To evaluate the functional dimension of family support, participants were asked to answer five questions related to family function through the Family APGAR questionnaire. APGAR assesses functional components of Adaptability, Partnership, Growth, Affection, and Resolve through five questions designed to reflect the participant's view of the functional status of his/her family. For each question, the participant should rate from 0 (never) to 4 (always) he/she is satisfied with his/her family partnership, empathy, support, affection and interaction. The total score, which ranges from 0 to 20 points, is the sum of points for each question. Higher scores mean a highly functional family (Smilkstein et al., 1982). Family Apgar assesses participants' emotional component of functional family support (e.g., loving and empathy relationship).

Community Support

Community support was assessed by asking participants whether they received social assistance from community programs such as social service, elderly well-being centers, colleges or universities, a healthy system, and religious entities. They were also asked to indicate whether they provide community support by serving any of those programs in the last 12 months. Data was recorded as a dichotomic variable (yes or no) for each question about receiving and serving in community programs.

Brain-Derived Neurotrophic Factor Concentration

Blood samples were obtained at fasting morning within 15 days before the survey, at participants' house through forearm venipuncture using vacuum tubes, free of anticoagulants. Within 1 h after sampling, blood samples were centrifuged at 4000 × g for 10 min, and serum was frozen at –80°C until further analysis. Serum BDNF concentration was determined using the commercial Chemikine BDNF ELISA kit (MerckMillipore, Darmstadt/Germany), following the manufacturer's instructions. Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h at 4°C with the samples diluted 1:100 in sample diluent and standard curve ranging from 7.8 to 500 ng/ml of BNDF (Corrêa et al., 2015). Plates were then washed four times with wash buffer followed by the addition of biotinylated mouse anti-human BNDF monoclonal antibody (diluted 1:1000 in sample diluent), which was incubated for 3 h at room temperature (Corrêa et al., 2015). After washing, a second incubation with streptavidin-horseradish peroxidase conjugate solution (diluted 1:1000) for 1 h at room temperature was carried out (Corrêa et al., 2015). After adding substrate and stop solution, the amount of BDNF was determined (absorbance set at 450 nm) (Corrêa et al., 2015). Samples were analyzed in duplicate, and the intra and inter-assay coefficients of variation were 5.2% and 10.4%, respectively.

Outcome Measures

Cognitive Performance

Participants was evaluated using the Mini-Mental State Examination (MMSE) for global cognition, the semantic verbal fluency (number of animals per minute) and Digit Span Backward for working memory (five digits to be repeated in the reverse order, scoring five points in maximum) (Caramelli et al., 2007; Brucki and Nitrini, 2010).

Potential Confounders Variables

Possible confounding variables of the association between family function, social support, BDNF and cognitive performance included: (1) sociodemographic characteristics (age, sex, race, education level, and marital status), chronic diseases (self-report of hypertension, diabetes, coronary artery disease, heart failure, pulmonary disease, and stroke), use of medication, smoking (current or previous), alcohol abuse (Michigan Alcohol Screening Test > 2), physical activity (self-report of regular physical activity in the last three months) and depression symptoms (Geriatric Depression Scale with 30 questions – GDS-30) (Yesavage et al., 1982). GDS-30 is a self-report instrument used to identify symptoms of depression in older adults. Participants were asked to answer "yes" or "no" for how they felt regarding enjoyment, interest, and social interactions over the past week. Positive or negative answers that indicate the presence of depression scored 1 point. Geriatric Depression Scale scores range from 0 to 30 points (Yesavage et al., 1982).

Statistical Analysis

We used mean, standard error (SE), and relative frequencies to describe sample characteristics, chronic diseases, use of medication, smoking, alcohol abuse, physical activity, family structure and community support. The association between cognitive performance and family and social support was tested using the Wald test (adjusted for sample weighted). To investigate the association between cognitive performance (e.g., MMSE, Verbal fluency, and Digit Span) and Family APGAR, we first examined the Pearson correlation coefficients between these variables followed by linear regression models adjusted for the potential confounders (as listed previously). Associations with a p-value of 0.2 or less in the univariate analysis were selected for the multiple regression analysis, in which forward selection was used (Bursac et al., 2008). The Stata 10® program (StataCorp,

TABLE 1 | Demographic characteristics, health evaluation and cognitive performance of the participants.

	Sample n	Mean (SE) or %	95% CI Min. – Max.
Demographic characteristics			
Age (years)	386	63.2 ± 0.98	62.96114 – 63.35825
Education status (years)	374	9.8 ± 0.28	9.301107 – 10.4566
Sex (% female)	386	54.4	–
Race (%)	386		
White		50.8	–
Brown		38.2	–
Black		8.2	–
Others		2.8	–
Marital status (%)	386		–
Divorced		15.0	–
Widowed		11.6	–
Married		66.2	–
Single		7.2	–
Health evaluation			
Hypertension (% yes)	386	57.2	–
Diabetes (% yes)	386	25.5	–
Cardiac disease (% yes)	386	17.7	–
Chronic Pulmonary disease (% yes)	386	8.7	–
Stroke (% yes)	386	5.8	–
Medication use (% yes)	386	9.0	–
Current Smoking (% yes)	386	19.7	–
Alcohol abuse (% yes)	386	5.2	–
Physical activity (% yes)	386	33.8	–
Geriatric Depression scale	374	10.2 ± 0.14	9.952732 – 10.52298
Cognitive performance and BNDF			
Mini-Mental State Exam	377	25.0 ± 0.29	24.41897 – 25.60125
Verbal fluency	382	14.4 ± 0.31	13.74534 – 15.00092
Digit span	385	4.0 ± 0.13	3.753055 – 4.279692
BDNF (ng/ml)	309	29.1 ± 11.1	27.74795 30.45865
Structural and Functional Family Support			–
Number of people living together	386	2.9 ± 1.6	2.746828 3.128288
Live alone (% yes)	386	12.1	–
Stay alone most of the time during the day (% yes)	386	22.1	–
Family Apgar	382	16.7 ± 0.27	16.2 17.3
Community Support	385		–
Receive community support (% yes)		4.8	–
Serve the community (% yes)		27.3	–

College Station, Tx) was used for all data analysis. The level of statistical significance was set at 0.05 and 95% CI.

RESULTS

Participant Characteristics

Participants were predominantly female, between 60 and 64 years old, and with a medium education level. Hypertension and diabetes were the most chronic diseases reported, and almost 20% had a smoking history. Most older adults lived with their partner and children, who used to help them with housework, outside activities, and self-care when necessary. However, almost 20% of them stayed alone most of the time during the day. The majority did not use community support, but more than a quarter served their community (**Table 1**).

Association Between Social Support, Brain-Derived Neurotrophic Factor, and Cognitive Performance

As previously described, social support was assessed through community support (receiving and offering) and family support (structural and functional). Regarding community support, the participants who offered support in their community showed

TABLE 2 | Association between family structure, community support, BDNF and cognitive performance (n = 386).

Variables	Structural family support						Community support					
	Lives alone mean (± SD)			Stays alone mean (± SD)			Receives support mean (± SD)			Offers support mean (± SD)		
	yes	no	*p*	Yes	no	*p*	yes	No	*p*	Yes	No	*p*
BDNF ng/ml	27.8 (10.1)	29.3 (11.4)	0.419	30.7 (11.5)	28.7 (11.2)	0.164	31.2 (13.3)	29.0 (11.2)	0.547	29.8 (10.1)	28.8 (11.8)	0.490
Verbal fluency	13.9 (4.6)	14.4 (4.1)	0.513	13.8 (4.3)	14.5 (4.1)	0.260	11.7 (4.9)	14.4 (4.1)	0.180	15.4 (4.3)	13.9 (3.9)	0.006
Digit Span	4.3 (1.6)	3.9 (1.6)	0.07	4.2 (1.5)	3.9 (1.6)	0.272	4.0 (1.4)	3.9 (1.6)	0.983	4.4 (1.2)	3.8 (1.7)	<0.001
MMSE	25.7 (3.0)	24.9 (3.9)	0.138	25.4 (3.3)	24.8 (4.0)	0.213	24.4 (3.0)	25.0 (3.9)	0.562	26.6 (3.0)	24.4 (4.0)	<0.001

MMSE, Mini-Mental State Exam; BDNF, Brain Derived Neurotrophic Factor – n = 309.

higher verbal fluency, digit span, and MMSE scores than those who did not serve. No difference was observed between those who received or not received support from the community (**Table 2**). Concerning the Structural Family Support, the older adults who live alone or stay alone most of the time showed similar BDNF levels and scores on cognitive tests compared to those who did not (**Table 2**). Similarly, family size (another component of structural family support) was not correlated with BDNF, verbal fluency, and digit span (**Table 3**). However, for family function component, the higher the Family Apgar, the higher the MMSE, Verbal fluency, and digit span scores (**Table 3**). Moreover, the multivariate analysis showed that MMSE, verbal fluency, and digit span scores' variability were significantly explained by the family Apgar, even controlling for age, education, sex, and depression symptoms (**Table 4**).

DISCUSSION

Using data from a population-based cohort, we explored the associations between family and community support and cognitive performance. A key finding was that functional family support, but not structural, was associated with better global cognition, verbal fluency and working memory, even controlling for potential cofounders. A second key finding was that providing support to the community, rather than receiving support from others, was associated with better cognitive performance. Brain-derived neurotrophic factor concentration was not associated with community support, family function, or cognitive performance. These findings suggest that emotional components of functional family and community support (e.g., loving and empathic relationship) may be more significant to cognitive health than size and frequency of social interactions.

Postulated mechanisms through which social relationships might impact cognitive aging include qualitative aspects of one's social relationships (Southwick et al., 2005). In that regard, our finding demonstrated that the higher the participant's satisfaction with their family partnership, empathy, support, affection and interaction, the better their cognitive performance. Contradicting other studies with the U.S. and Chinese population (Sims et al., 2014; Ge et al., 2017; Li et al., 2019), our findings that high emotional support was associated with better cognitive performance is consistent with much evidence reporting protective effects of functional support on cognition (Seeman et al., 2001; Windsor et al., 2014; Kelly et al., 2017; Ying et al., 2020; Costa-Cordella et al., 2021). Social interactions are cognitively and emotionally processed by the brain, socially supportive interactions may contribute to better cognitive aging through direct positive stimulatory effects on the brain (Seeman et al., 2001). In line with that, social networks, community engagement are associated with a lower risk of cognitive impairment and dementia (Salinas et al., 2017).

In contrast to previous studies, we did not find an association between cognitive performance and instrumental social support (i.e., receiving assistance/help from others). However, we observed that participants who provided support to their community showed higher performance on global cognition, verbal fluency and working memory performance, suggesting different effects of social support and social activity on specific cognitive domains. Supporting that interpretation, social support was demonstrated to be associated with benefits to episodic memory (Hughes et al., 2008; Kelly et al., 2017), which was not assessed in participants from the SABE study. While social activity (i.e., develop any activity in the community) was most consistently associated with improvements in global cognition and working memory (Plehn et al., 2004; Kelly et al., 2017), that are cognitive domains essential for navigating the complexities of the social world demands (Meyer and Lieberman, 2012). In addition, altruistic behavior seems to have a role in older adults' cognition, with more altruistic characteristics associated with greater global cognition and verbal fluency, while volunteering was not (Correa et al., 2019). One explanation for the different effects of social support versus social activity may be the impact of social support on stress. Social support has been shown to promote resilience against the negative consequences of stress (Ozbay et al., 2007), whereas simply engaging in social activities or reporting a larger network of family and friends may not translate to the kind of social-emotional support required to obtain such stress-reducing benefits. To promote brain health, our findings allied to previous studies highlight that social support and engagement in social activity may differently impact cognitive domains depending on whether the intervention purpose is to reduce stress or to produce brain stimulation.

Regarding the biological mechanisms explaining how social support and social relationships influence cognition, we did not confirm the hypothesis that higher BDNF levels are associated

TABLE 3 | Pearson's correlation coefficients between Family APGAR, BDNF, cognitive performance and potential covariates.

	Correlation's coefficient								
	Verbal fluency	**Digit Span**	**MMSE**	**Age**	**Education**	**GDS**	**BDNF**	**Family Apgar**	**Family size**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	–								
2	0.212**	–							
3	0.298**	0.495**	–						
4	–0.055	0.016	–0.012	–					
5	0.187**	0.238**	0.323**	–0.048	–				
6	0.103*	0.048	0.173	–0.043	0.108*	–			
7	0.032	–0.058	0. 024	0.065	–0.114*	0.035	–		
8	0.236**	0.183**	0.235**	–0.009	0.085	0.247**	0.010	–	
9	–0.048	–0.061	–0.134**	0.051	–0.095	–0.047	–0.025	0.026	–

**p < 0.05 and **p < 0.001. Family size = number of relatives living together with the participant. MMSE = Mini-Mental State Exam; Geriatric Depression Scale; BDNF[a] = Brain Derived Neurotrophic Factor – n = 309.*

TABLE 4 | Multivariate regression coefficients between Family APGAR, BDNF and cognitive performance, adjusted for covariates.

Variables	**MMSE n^1 = 287 n^2 = 362**					**Verbal fluency n^1 = 292 $n^{2=}$ 370**					**Digit Span n^1 = 298 $n^{2=}$ 370**				
	B	***p***	**R^2**	**F**	***P***	**B**	***p***	**R^2**	**F**	***P***	**B**	***p***	**R^2**	**F**	***p***
Model 1			0.98	1480.5	<0.001			0.93	342.6	<0.001			0.89	384.9	<0.001
Age	0.249	< 0.001				0.102	0.001				0.034	0.001			
Education	0.365	< 0.001				0.267	0.012				0.102	0.006			
Sex	0.106	0.742				0.394	0.444				0.248	0.218			
GDS	0.192	0.068				0.069	0.557				0.023	0.696			
Family APGAR	0.189	< 0.001				0.214	< 0.001				0.053	0.010			
BNDF[a]	0.023	0.160				0.026	0.185				0.003	0.738			
Model 2			0.98	3669.5	< 0.001			0.88	767.6	< 0.001			0.88	612.8	< 0.001
Age	0.294	< 0.001				0.132	< 0.001				0.034	< 0.001			
Education	0.374	< 0.001				0.229	0.012				0.110	0.001			
Family APGAR	0.177	< 0.001				0.221	0.001				0.048	0.004			

Model 1 adjusted for all covariates; n^1 = number of participants in model 1; Model 2 adjusted only for covariates with p < 0.2; n^2 = number of participants in model 2; GDS = Geriatric Depression Scale; BDNF[a] = Brain Derived Neurotrophic Factor.

with higher social support and better cognitive performance. In contrast, Salinas et al. (2017) observed that social isolation trended with lower serum BDNF after controlling for age and sex; meanwhile, having someone available to provide emotional support most or all of the time was associated with higher BDNF and lower dementia risk (Salinas et al., 2017). Although serum BDNF is considered an indirect measure of central nervous system levels (Laske et al., 2007), peripheral pro-BDNF/mBDNF ratio (Cechova et al., 2020), or postmortem BDNF levels may provide different findings. In addition, BDNF changes over time may better capture the protective role mediating social activity and cognitive functioning (Salinas et al., 2017).

Although this study has provided some interesting findings, certain limitations must be considered in interpretating results. First, the associations in this study were based on a cross-sectional design, and reverse causation interpretation is a possibility. Patients with mild cognitive impairment, which is underdiagnosed in the elderly community (Sternberg et al., 2000; Brayne et al., 2007), tend to lose social ties and engagement in community activities. Thus, participants with better cognitive performance were more likely to participate in social activities and provide community support than those with worse cognitive abilities. On the other hand, those participants would also be more likely to receive social support throughout the health system and community entities to handle their cognitive losses, which was not observed in the present study. Furthermore, no measures BDNF gene variants were analyzed. Existing data support a possible effect of BDNF polymorphisms, mainly C270T and Val66Met on the risk of Alzheimer's disease (AD) (Kunugi et al., 2001; Riemenschneider et al., 2002; Ventriglia et al., 2002). Moreover, no measures of stress were evaluated and should be considered in future studies as both social support and cognition may be influenced by psychological and biological mediators of stress (Juster et al., 2010). Finally, longitudinal data from the SABE study may confirm whether better cognitive performance related to social support at the begging of aging constitutes

a protective factor and predictor of successful cognitive aging in later life.

Despite these limitations, our study is unique regarding several relevant aspects. The current findings extend previous research by showing that functional social support (i.e., quality of family relationship and community activity) is a better predictor of global cognition and executive function performance than the structural dimension of social support (i.e., size and frequency of interaction). Moreover, data was based on probabilistic sampling from the most populous cities in Latin America, where the prevalence of dementia is projected to increase dramatically in the next few years (Ferri and Jacob, 2017). Heterogenous education and income backgrounds, allied to cultural characteristics of family ties, whose relationships extend the nuclear members, represent unique social contexts to investigate interaction opportunities and understand its impact on cognition. This study may represent an initial attempt to explore further social and family factors capable of influencing cognitive performance and successful aging.

In summary, our study revealed that, compared to structural social support, function family support and community activity are associated with better global cognition and executive function performance. These findings may inform future studies to investigate whether family relationships and support represent a protective factor for the risk to develop cognitive impairment and dementia in more vulnerable populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Human Research Ethics Committee of the University of Sao Paulo Faculty of Public Health (#COEP/23/10), São Paulo, Brazil. All participants provided written informed consent.

AUTHOR CONTRIBUTIONS

JS-T and EB designed and wrote the study protocol, managed the literature searches and analyses, and wrote the final draft of the manuscript. JS and YD are the SABE study PIs, coordinate all study steps from sampling, recruitment, data collection, data management, and data analysis. BF and DS manage literature searches, manage data, and performed BDNF analysis. All authors critically reviewed and approved the final version of the manuscript.

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