

## ORIGINAL RESEARCH—INTERSEX AND GENDER IDENTITY DISORDERS

### Hormonal Treatment Reduces Psychobiological Distress in Gender Identity Disorder, Independently of the Attachment Style

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#### ABSTRACT

**Introduction.** Gender identity disorder may be a stressful situation. Hormonal treatment seemed to improve the general health as it reduces psychological and social distress. The attachment style seemed to regulate distress in insecure individuals as they are more exposed to hypothalamic–pituitary–adrenal system dysregulation and subjective stress.

**Aim.** The objectives of the study were to evaluate the presence of psychobiological distress and insecure attachment in transsexuals and to study their stress levels with reference to the hormonal treatment and the attachment pattern.

**Methods.** We investigated 70 transsexual patients. We measured the cortisol levels and the perceived stress before starting the hormonal therapy and after about 12 months. We studied the representation of attachment in transsexuals by a backward investigation in the relations between them and their caregivers.

**Main Outcome Measures.** We used blood samples for assessing cortisol awakening response (CAR); we used the Perceived Stress Scale for evaluating self-reported perceived stress and the Adult Attachment Interview to determine attachment styles.

**Results.** At enrollment, transsexuals reported elevated CAR; their values were out of normal. They expressed higher perceived stress and more attachment insecurity, with respect to normative sample data. When treated with hormone therapy, transsexuals reported significantly lower CAR ( $P < 0.001$ ), falling within the normal range for cortisol levels. Treated transsexuals showed also lower perceived stress ( $P < 0.001$ ), with levels similar to normative samples. The insecure attachment styles were associated with higher CAR and perceived stress in untreated transsexuals ( $P < 0.01$ ). Treated transsexuals did not expressed significant differences in CAR and perceived stress by attachment.

**Conclusion.** Our results suggested that untreated patients suffer from a higher degree of stress and that attachment insecurity negatively impacts the stress management. Initiating the hormonal treatment seemed to have a positive effect in reducing stress levels, whatever the attachment style may be. **Colizzi M, Costa R, Pace V, and Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. J Sex Med 2013;10:3049–3058.**

**Key Words.** Gender Identity Disorder; Hormonal Sex-Reassignment Therapy; Cortisol Awakening Response; Perceived Stress; Adult Attachment; Transsexualism

#### Introduction

Cross-sex hormone treatment is an important component in the medical treatment of transsexual people and is desired by patients to successfully live as a member of their identified gender. It provides some relief from the dichotomy between body habitus and gender identity. For this reason, hormone therapy seems to

give a feeling of social re-adaptation that alleviates the suffering of transsexuals and to facilitate the distress reduction [1]. This is particularly important for those transsexuals who experience insecure relations and are more vulnerable to the stress system dysregulation. In fact, the conditions that promote the development of an insecure attachment in relations are also associated with the dysregulation of the stress response [2].

The gender identity disorder (GID) is characterized by a strong and persistent identification with the opposite sex and persistent discomfort with one's own biological sex or the roles assigned to it [3]. GID or transsexualism may also be suspected in children; therefore, in adolescents and young adults, this condition may be a continuation of a previous condition or develop *de novo*. A distinction should be made between transsexualism and other conditions that are not characterized by a persistent desire of a permanent sex change. Transsexualism cannot be diagnosed if the individual has a concurrent physical intersex condition such as androgen insensitivity syndrome or congenital adrenal hyperplasia. Transient and stress-related cross-dressing behavior, as well as a persistent preoccupation with castration or penectomy without a desire to acquire the sex characteristics of the other sex, is not sufficient to diagnose transsexualism either. All these conditions are diagnosed as GID not otherwise specified [3].

For most patients, transsexualism may be a stressful condition and may cause clinical distress or impairment in important areas of functioning [4,5]. Several studies, including a meta-analysis, indicated that cross-sex hormonal intervention improves quality of life and overall happiness among transsexual individuals [6,7]. Hormones contributed to optimizing the real life process in the sex identity, improving the well-being, and decreasing the psychiatric comorbidities often associated with a lack of hormone treatment [1]. Motmans et al. showed that hormonal treatment has improved transsexuals' general health, while there was no significant difference in the quality of life between transsexuals who had undergone genital or breast surgery and transsexuals who did not have these surgeries, suggesting the centrality of hormonal treatment [8]. Specifically, a recent study has shown that patients under cross-sex hormonal treatment reported a lower prevalence of perceived social distress than patients who had not initiated hormone therapy, suggesting a positive effect of hormonal treatment in the management of psychological and sociological distress in transsexual patients [9].

The normal function of attachment is to regulate distress and stressful situations stimulate the attachment system thus activating physiological responses [10,11]. The quality of the parental style, as well as the family life events during infancy, determines the attachment style [12] and outlines durable cognitive schemes of care expectancy that persist in adult life [10,13,14]. A connection between the subjective differences in coping with the stressful situ-

ations and with the psychological distress [14], and the attachment styles has been proved by studies.

The hypothalamic–pituitary–adrenal (HPA) axis abnormality has been reported to be a characteristic consequence of frequently repeated or chronic environmental stress challenges. Chronic stress-induced stimulation of HPA activity alters adrenocorticotrophic hormone (ACTH) secretagogue expression and hypothalamic afferent activity to maintain adrenocortical responsiveness [15]. Dysregulation of these control mechanisms ensues. The consequent overriding function of a pathological HPA axis determines a persistent increase of cortisol awakening response (CAR) and of daily cortisol plasmatic levels, especially in individuals with an insecure style of attachment (anxious or avoidant), and for this reason unable to face stressful situations [16–18]. Stress-induced hypercortisolism seemed to establish risk factor for a variety of diseases and increase the all-cause mortality risk of affected subjects by twofold to threefold, curtailing their life expectancy by several years [19,20].

There have been several studies into the possible positive effects of surgical therapy [21,22]; in contrast, the literature on the effect of cross-sex hormone therapy on psychobiological parameters is more limited.

To our knowledge, quantitative data on perceived and biological stress and differences in its regulation related to the hormonal treatment have not been previously reported. Moreover, no research has been carried out to investigate attachment among adults with transsexualism and, more specifically, the presence of insecure conditions with regard to psychobiological distress.

If transsexualism seems to be a stressful condition, insecure attachment and hormonal therapy may determine a clinically increase or reduction of CAR and perceived stress levels, respectively, with important consequences for therapeutic interventions.

The objective of the present study was to evaluate the presence of current psychobiological distress in transsexuals attending a gender identity unit through the CAR and perceived stress measurement. We compared these values with regard to the hormonal intervention. On the basis of previous research and of our own clinical experience, we suggested a significant reduction of CAR and perceived stress in transsexuals after the beginning of hormonal treatment. Within a theoretical framework and inspired by the attachment theory, we also suggested the insecure attachment styles be significantly associated with higher CAR and perceived stress if compared with the secure style. Finally, we

tested the interaction between attachment styles and hormone therapy on CAR and perceived stress to see whether stress levels in different attachment styles in untreated and treated transsexual patients differ.

## Materials and Methods

### Participants

Seventy consecutive patients have visited the Gender Identity Unit of the University of Bari Psychiatric Department between 2008 and 2011. Each patient has been visited by two psychiatrists with a special interest in this topic, one of whom is author of this study (O.T.). Each patient has received psychological counseling and has been interviewed according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) as he manifested all the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR) diagnostics criteria for GID in adults. The presence of any neurologic or psychiatric pathology and of any metabolic or intersexual pathology (as diagnosed by the endocrinologist and accompanied by hematologic and chromosome profile evaluations) has been considered an exclusion principle. All patients have signed the informed consent for data treatment. Forty-five (64%) belonged to the male to female (MtF) type. Hormonal treatment for MtF transsexuals consisted of transdermal estradiol gel ( $1.77 \pm 0.46$  mg/day), in association with oral cyproterone acetate (100 mg/day). The androgen administration schedule in female to male (FtM) patients consisted of testosterone administered as intramuscular injections of a testosterone esters depot (250 mg every  $27.12 \pm 2.64$  days). All the patients in this study received hormonal therapy. The unit has adopted the standards of care guidelines of the World Professional Association for Transgender Health [23]. No patient had undergone any type of surgical intervention.

### Measurement of CAR

CAR was measured by taking a blood sample of 20 mL per patient at 8:00 AM, 1 hour after wake up, for 3 consecutive days, once before the onset of hormone therapy (phase 1), and once after about 12 months ( $52.14$  weeks  $\pm 17.1$  days) of hormone therapy (phase 2). All the patients performed these evaluations. For each patient, in phase 1 and in phase 2, a mean of the three CARs was calculated. At the moment of each blood taking, all patients

had fasted for at least 8 hours, had not drunk caffeine or alcohol nor smoked since the previous night, and neither had they practiced any hard physical exercise during the 3 days before. While awakening cortisol levels seemed to be comparable across the female menstrual cycle phases, without significant differences in the CAR between the follicular and luteal phase, researches have shown a net increase during ovulation, presumably mediated by elevated sex steroid levels during the ovulation period [24]. For this reason, at the time of the evaluation, the FtM patients did not have the menstrual cycle and were far from the timing of ovulation. The samples were collected in the days immediately after menstruation. None of the patients had taken medical/recreational drugs for 6 months. The CAR was obtained by using an automated analyzer with chemiluminescent immunometric assay according to manufacturer's recommendations. In this study, we have decided to evaluate the CAR because it is associated with various health conditions and risk factors and it is a distinct measure of the circadian cortisol rhythm. It has repeatedly been suggested that the CAR could be a result of the stress anticipation and could support coping with daily life stress [25].

### Measurement of Perceived Stress

All the patients performed a self-reported evaluation of perceived stress. They assessed this evaluation in phase 1 (before), when they were still waiting for hormone therapy approval, and in phase 2 (after hormone therapy). Each of these two investigations was conducted before the first cortisol measurement. The perceived stress has been evaluated by the 10-item Perceived Stress Scale (PSS) [26]. It is the most commonly used measure of perceived stress. Answers to the 10-item PSS were summed for each participant, yielding scores that ranged from 0 (*low perceived stress*) to 40 (*high perceived stress*). A recent study has reviewed several articles related to the psychometric properties of the PSS. This search has found that internal consistency reliability, factorial validity, and hypothesis validity of the PSS were well reported. The test-retest reliability and criterion validity were evaluated too, though to a lesser extent. The 10-item version is suggested as it has maximum reliability. In this study, we used the 10-item PSS whose psychometric properties also were found to be superior to those of the 14-item PSS, while those of the four-item scale fared the worst [27]. Appropriate application of this instrument in epidemiological and clinical research, as well as in

inpatient care, can aid the detection of psychosocial stress and ensure accurate identification of individuals who would benefit from specific psychotherapeutic interventions [28].

### Measurement of Attachment

The attachment styles have been assessed through the Adult Attachment Interview (AAI) [29] by one of the authors who is an expert psychologist-psychotherapist with certification (V.P.). Only 50 participants were well disposed toward this particular interview. The AAI is a semistructured interview that explores the representation of attachment in the adult by a backward investigation in the relations between the child and the parental figures. The AAI is audio recorded and transcribed verbatim. This transcript has made it possible to classify the current mental state of an adult in relation to his/her attachment history by evaluating the coherence between emotions and thoughts. The AAI helps distinguish four styles of attachment: secure (safe and balanced), avoidant (the importance given to relation is minimum), anxious (worry, ambivalence, and rage), and unresolved/disorganized (due to traumas coming from loss or abuse). In this study, we have decided to use the AAI first because attachment represents the person's early experiences that are crucial in the development of the stress system and then because it shows relative stability from infancy to adulthood and is fundamental in stress management and HPA axis regulation [10,11,30,31]. Subjects with the avoidant or the anxious attachment style are both considered insecure. The unresolved/disorganized attachment style, instead, is used if the interview shows signs of unresolved experiences of trauma usually involving the loss of attachment figures. Therefore, this style is superimposed on the three main classifications [32]. Rigorous psychometric testing and meta-analyses of the AAI demonstrate stability and discriminant and predictive validity in both clinical and non-clinical populations [33,34] and in Italian samples too [35]. The test-retest stabilities of the secure, avoidant, and anxious categories are 77–90% across 1- to 15-month periods [33,36] and are not attributable to interviewer effects [37].

### Statistical Analysis

Statistical analysis was conducted using STATA 10 (Stata Corp, Georgetown, TX, USA). The difference of the proportion of MtF and FtM transsexual patients among occupational status, as well as the proportion of transsexual patients and normative

samples among attachment styles, was evaluated using the chi square. The comparison of age and level of education between MtF and FtM, as well as the comparison of CAR and perceived stress between treated and untreated transsexuals, was performed using independent sample *t*-tests. *t*-Tests were used to compare the perceived stress between treated/untreated transsexual patients and normative sample. Interactions of hormonal treatment and attachment styles on CAR/perceived stress were evaluated using two-way analysis of variance. Fisher's post hoc description was applied if differences were found. The significance level was set at  $P < 0.05$ .

### Ethics

The study was approved by the Ethics Committee of the Medical Faculty, University of Bari.

### Results

#### The Demographic Variables

The average age of the sample did not show significant differences between MtF (mean = 29.25 years, standard deviation [SD] = 9.87) and FtM patients (mean = 26.78 years, SD = 8.09) ( $t = 0.90$ ;  $P = 0.37$ ). No significant differences emerged between the level of education of MtF (mean = 11.6 years of study, SD = 1.21) and FtM (mean = 10.3 years of study, SD = 1.61) ( $t = 7.83$ ;  $P = 0.49$ ) and between their occupational status (31 MtF [69%] and 18 FtM [72%] employed) ( $\chi^2 = 0.07$ ,  $P = 0.79$ ).

#### CAR

In phase 1, patients showed elevated CAR (mean = 28.98  $\mu\text{g/dL}$ , SD = 20.82  $\mu\text{g/dL}$ ); in fact, the values were out of the normal range (normal value: 9–23  $\mu\text{g/dL}$ ). There were no significant differences between untreated MtF (mean = 31.71  $\mu\text{g/dL}$ , SD = 16.48  $\mu\text{g/dL}$ ) and untreated FtM (mean = 27.78  $\mu\text{g/dL}$ , SD = 26.76  $\mu\text{g/dL}$ ). In phase 2, patients expressed significantly lower CAR (mean = 15.72  $\mu\text{g/dL}$ , SD = 6.54  $\mu\text{g/dL}$ ) ( $t = 4.25$ ,  $P < 0.001$ ). There were no significant differences between treated MtF (mean = 15.94  $\mu\text{g/dL}$ , SD = 6.42  $\mu\text{g/dL}$ ) and treated FtM (mean = 15.23  $\mu\text{g/dL}$ , SD = 6.74  $\mu\text{g/dL}$ ) (Table 1).

#### Perceived Stress

In phase 1, patients expressed elevated levels of perceived stress, as evidenced by a high average total PSS score (mean = 27.70, SD = 6.11). There



**Table 1** Means, standard deviations, and statistical comparisons with *t*-test of the relationship between cortisol awakening response and cross-sex hormonal treatment in transsexual patients

	Transsexuals without hormonal treatment (N = 70) M (SD)	Transsexuals under hormonal treatment (N = 70) M (SD)	<i>t</i> -Test	
			<i>t</i>	<i>P</i>
CAR (9–23 µg/dL)	28.98 (20.82)	15.72 (6.54)	4.25	0.001

CAR = cortisol awakening response; M = mean; SD = standard deviation

were no significant differences between untreated MtF (mean = 29.13, SD = 6.05) and untreated FtM (mean = 25.37, SD = 5.71). When comparing the perceived stress found in our sample with the available normative data [26], it was clear that, in transsexual patients, perceived stress was considerably higher than in nonclinical samples of the same age (mean = 14.2, SD = 6.2) ( $t = -17.53$ ;  $P < 0.001$ ). In phase 2, transsexual patients showed a significantly lower perceived stress (mean = 14.96, SD = 4.89) ( $t = 11.51$ ,  $P < 0.001$ ), coinciding almost perfectly with that found in nonclinical samples of the same age ( $t = -1.2$ ;  $P = 0.12$ ). There were no significant differences between treated MtF (mean = 14.67, SD = 4.83) and treated FtM (mean = 15.42, SD = 5.08) (Table 2).

### Attachment Patterns

Transsexual patients showed a high percentage of insecure attachment (70%). Twenty-three patients showed avoidant attachment (46%), 11 the anxious type (22%), 1 the unresolved/disorganized type superimposed on the anxious type (2%), and only 15 the secure type (30%). Moreover, when comparing the attachment styles found in our sample with the available normative data about nonclinical young adults and clinical groups of the same age [32], we found that the percentage of insecure conditions in the group of participants with transsexualism was considerably higher than that usually found in nonclinical samples ( $\chi^2 = 9.91$ ,  $P = 0.002$ ) and clinical groups ( $\chi^2 = 4.81$ ,  $P = 0.03$ ). When

classifying participants with transsexualism on the basis of one of the three attachment styles (secure, avoidant, and anxious), the distribution of percentages also differed significantly from that found in nonclinical ( $\chi^2 = 9.45$ ,  $P = 0.009$ ) and clinical samples ( $\chi^2 = 6.12$ ,  $P = 0.046$ ). The main difference was in the percentage of those with a secure attachment style, which is lower in the case of participants with transsexualism (30%) as compared with clinical (46%) and nonclinical samples (56%) (Table 3). Only one patient has shown an unresolved/disorganized attachment (phase 1: PSS 27, CAR 14.2; phase 2: PSS 23, CAR 13.2) and has been excluded from the analysis.

### Interaction of Attachment Styles and Hormonal Treatment on CAR

There was a significant interaction between the attachment patterns and the hormone therapy on CAR ( $F = 3.97$ ,  $P = 0.02$ ) (Figure 1). In phase 1, anxious patients showed significantly higher CAR (M = 42.94 µg/dL, SD = 33.77 µg/dL) than avoidant (M = 26.73 µg/dL, SD = 14.74 µg/dL) ( $F = 5.39$ ,  $P = 0.003$ ) and secure patients (M = 22.21 µg/dL, SD = 10.96 µg/dL) ( $F = 5.83$ ,  $P < 0.001$ ). In phase 2, there were no significant differences in CAR by attachment. In contrast to anxious (M = 14.69 µg/dL, SD = 4.81 µg/dL) and avoidant patients (M = 15.69 µg/dL, SD = 7.28 µg/dL), secure patients (M = 16.51 µg/dL, SD = 6.75 µg/dL) did not show significant differences in CAR between phase 1 and phase 2.

**Table 2** Means and standard deviations of the perceived stress measured with the Perceived Stress Scale in transsexual patients without and under cross-sex hormonal treatment and in normative samples, and statistical comparisons with *t*-test

	Transsexuals without hormonal treatment (N = 70) M (SD)	Transsexuals under hormonal treatment (N = 70) M (SD)	Normative samples (N = 645) M (SD)	<i>t</i> -Test	
				<i>t</i>	<i>P</i>
PSS (0–40)	27.70 (6.11)	14.96 (4.89)	14.2 (6.2)	-17.53*	<0.001
				11.51†	<0.001
				-1.2‡	0.12

\*Comparison between transsexuals without hormonal treatment and normative samples

†Comparison between transsexuals without and under hormonal treatment

‡Comparison between transsexuals under hormonal treatment and normative samples

M = mean; PSS = Perceived Stress Scale; SD = standard deviation

**Table 3** Prevalence of attachment styles and overall insecure attachment (anxious and avoidant styles) measured with Adult Attachment Interview in transsexual patients, in normative clinical and nonclinical groups, and statistical comparisons with chi square

	Transsexuals (N = 70) N (%)	Normative clinical group (N = 1,023) N (%)	Normative nonclinical group (N = 861) N (%)	Chi square	
				$\chi^2$	P
Attachment styles				6.12*	0.046
Secure	15 (30%)	471 (46%)	482 (56%)	9.45†	0.009
Anxious	12 (24%)	133 (13%)	146 (17%)		
Avoidant	23 (46%)	419 (41%)	233 (27%)		
Insecure attachment (anxious and avoidant)	35 (70%)	552 (54%)	379 (44%)	4.81*	0.03
				9.91†	0.002

\*Comparison between transsexuals and normative clinical group

†Comparison between transsexuals and normative nonclinical group

### Interaction of Attachment Styles and Hormonal Treatment on Perceived Stress

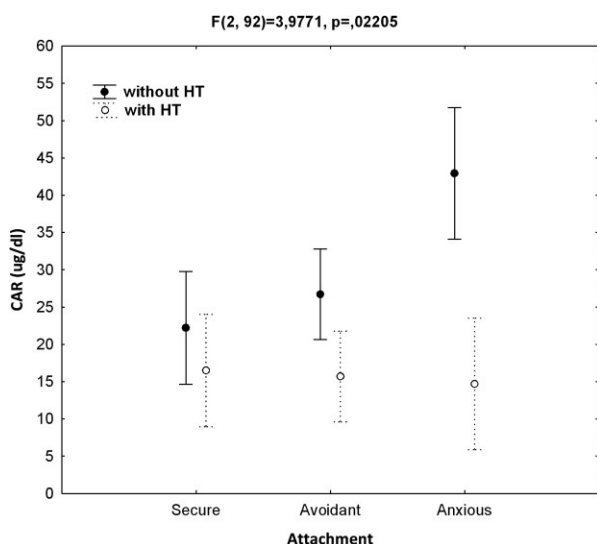
There was a significant interaction between the attachment conditions and the hormone therapy on perceived stress ( $F = 4.98$ ,  $P < 0.01$ ) (Figure 2). In phase 1, anxious patients expressed significantly higher perceived stress ( $M = 33.09$ ,  $SD = 5.28$ ) if compared with avoidant ( $M = 28.17$ ,  $SD = 4.65$ ) ( $F = 1.85$ ,  $P = 0.009$ ) and secure patients ( $M = 23.26$ ,  $SD = 5.61$ ) ( $F = 2.00$ ,  $P < 0.001$ ). Also avoidant patients showed significantly higher perceived stress than secure patients ( $F = 1.67$ ,  $P = 0.004$ ). In phase 2, there were no significant differences in perceived stress by attachment (anxious style:  $M = 15.27$ ,  $SD = 4.71$ ; avoidant

style:  $M = 15.30$ ,  $SD = 5.04$ ; secure style:  $M = 14.4$ ,  $SD = 5.13$ ). All the three attachment styles showed significant differences in perceived stress between phase 1 and phase 2 (anxious style:  $F = 2.15$ ,  $P \leq 0.001$ ; avoidant style:  $F = 1.49$ ,  $P \leq 0.001$ ; secure style:  $F = 1.84$ ,  $P \leq 0.001$ ).

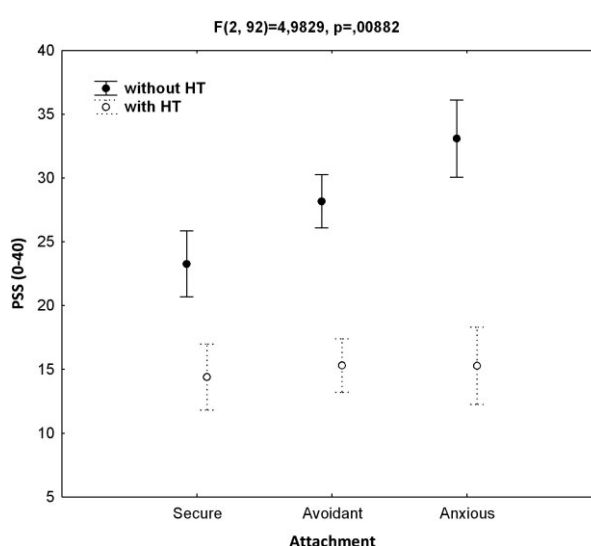
### Discussion

The study aimed at describing the presence of psychobiological distress and attachment insecurity in transsexual patients.

Results from this study indicated that these patients show HPA dysregulation and appear to notably differ from the normative samples in terms



**Figure 1** Interaction between hormonal treatment and attachment styles on cortisol awakening response in transsexual patients. CAR = cortisol awakening response; HT = hormonal treatment



**Figure 2** Interaction between hormonal treatment and attachment styles on perceived stress in transsexual patients. HT = hormonal treatment; PSS = Perceived Stress Scale

of mean levels of perceived stress and percentage of attachment insecurity. They showed elevated CAR, with cortisol levels above the normal range, and elevated perceived stress, confirming the literature data on distress related to transsexualism [4,5]. They expressed also a high percentage of attachment insecurity.

An important result of our study was that when treated with cross-sex hormone therapy, transsexuals reported significantly lower CAR, falling within the normal range for cortisol levels in the morning, and lower perceived stress, with levels similar to normative samples.

Another result from this study was that, as shown in the literature about healthy subjects, attachment insecurity and especially the anxious style seemed to be associated with CAR and perceived stress and consequently with psychobiological stress management [16,18].

The last and most interesting result from this study was that after about 12 months of hormonal treatment we did not find significant differences in perceived stress and CAR by attachment groups, suggesting that transsexual patients can improve their stress levels whatever the attachment style may be. Our data suggested that untreated patients suffer from a higher degree of stress and that attachment insecurity, especially the anxious pattern, negatively impacts the stress management. Interestingly enough, instead, secure patients did not show differences in CAR between phase 1 and phase 2 in both cases showing values in the normal range, and this finding suggested a protective effect of secure attachment against HPA dysregulation.

Despite the importance attributed to the problems connected to the attachment insecure styles in structuring numerous psychobiological alterations, there is little quantitative and categorical work about the attachment and the experience of social or emotional distress in children, adolescents, and adults with transsexualism. Some researches have been restricted to transsexual children and the parents of transsexual children. In particular, only one study has shown the existence of a prevalence of ambivalent attachment styles among children with this condition [38]. A research program has been conducted on the parents of transsexual children founding in the vast majority of cases parents with an insecure attachment style (avoidant or anxious) [39]. In addition, highly stressful factors or traumas were found in the primary attachment figures' history operating just before or during early childhood of transsexual patients [40]. Moreover, transsexual children have

shown, on average, more behavior and emotional problems than their siblings and controls [41]; they have also shown a high rate of traumatic experiences that may relate to specific transgenerational dynamics [42,43].

Frequent early-life stress like, for example, inadequate parental care and the subsequent insecure attachment style can have enduring effects on stress reactivity and on HPA system regulation, as evidenced by different studies [44–46]. Insecure early care-giving experiences stimulate up-regulation or down-regulation of adult cortisol stress responses resulting in dysregulation of stress responsivity [47]. The quality of parental caretaking is considered to be particularly crucial while brain systems critically involved in the regulation of the HPA axis such as the hippocampus or the prefrontal cortex are developing [48,49]. Accordingly, while high parental responsiveness and sensitivity during this period attenuates HPA reactivity throughout the life span [50,51] and promotes adequate biobehavioral regulation and well-being of the offspring in general [52–54], adverse early rearing conditions such as insensitive and unresponsive care [55] have been linked to increased HPA reactivity and poor biobehavioral regulation throughout the life span. Secure individuals, therefore, are generally able to develop efficient strategies to cope with stress. Instead, insecure patients with high levels of anxiety or avoidant attitude tend to adopt dysfunctional strategies. The insecure individuals are more likely to show emotional uneasiness because of stressful experiences. The HPA axis is activated in response to stressful situations having a strong emotional impact on an interpersonal level [56]. A difficult management of the stress and of the negative emotions ensues, and this is proved by a steady presence of high cortisol levels also a long time after the exposure to stress [57]. Moreover, the insecure behavior has been associated with a higher sense of solitude and social isolation and to greater relational difficulties [58]. The sense of solitude and the self-reported difficulty in managing stress have been connected with the CAR increase [59].

Over the course of the past decade, CAR as part of the circadian rhythm has extensively been investigated. It typically constitutes the circadian peak of cortisol secretion and has been identified as a reliable marker for studying individual differences [60]. Although the CAR has found to be related to a number of factors such as age, time of awakening, sleep quality, and genetic differences, the determinants of CAR have not been fully explained yet.

There is considerable evidence that the cortisol increase after awakening is reduced in individuals scoring high on personality dimensions that have been associated with high levels of attachment security [18]. According to our results, there appears to be an association between hormonal treatment and lower stress levels, also in insecure individuals. This result may have several explanations. First, the stress differences might be a direct effect of hormone therapy. As previously reported in only one study in MtF subgroup, estrogens may reduce cortisol levels in transsexuals: Mueller et al. found that cortisol levels were reduced by 43% after 12 months of estrogenic therapy in MtF patients [61]. According to the authors, cortisol serum levels may be decreased due to estrogen-induced increase in corticoid-binding globulin. We did not find researches about the effect of androgenic therapy in FtM patients. However, some studies suggested that testosterone levels are significantly associated with several measures of stress in women, perceived stress included [62]. Therefore, one would expect that treated MtF transsexuals might display lower cortisol and perceived stress levels than treated FtM. Nevertheless, our study did not find differences between MtF and FtM when gender was included in the statistical analyses. Therefore, our results could not support this hypothesis, and, in accordance with Kuiper and Cohen-Kettenis, there appears to be no direct relation between the hormone therapy itself and the patients' subjective well-being [63]. In any case, data are too limited to express conclusively. Second, stress in transsexuals may be considered as a reaction to the nonsatisfaction connected to their incongruent body image and, as hormone therapy induces desired changes in body features and shape, this could translate into a better quality of life for the patient himself. Thanks to the body changes obtained, transsexuals could experience a reduction of self-reported distress [9,64]. Third, the initiation of the hormonal treatment could have a psychological meaning which per se could be fundamental in reducing stress.

Further researches are needed to resolve these issues. Understanding these mechanisms is extremely important if one wants to grant early enough interventions to transsexuals who seem to live a very stressful condition. This article has showed the potential for early hormonal treatment intervention to reduce the deleterious effects of stress on the brain, behavior, and cognition. After years of research on the negative effects of stress, it is now time to turn our attention to the potential

positive impact of early interventions, especially in vulnerable patients. These results could help us develop health policies that treat the problem of early-life stress by promoting therapeutic actions that increase the patients' supportive experiences and sense of attachment security. As reported in previous studies, our clinical experience suggests that transsexual patients attending a gender unit are pleased in the knowledge that the hormonal therapy will be performed within a reasonable time and refer a distress reduction [63,64]; instead, transsexuals and in particular the insecure patients express distress when treatments are delayed because of their health problems. In fact, we suspect that findings would likely be different if therapy were discontinued or in patients who have no possibility of being attended by a gender unit.

A limit of our study was that we did not evaluate the cortisol levels in the rest of the day. A second limit of our research was that the normative data about perceived stress are collected in a sample from the USA, which may be not comparable with an Italian sample. Moreover, the generalization of our results may be limited by the fact that patients were recruited from a specialized gender unit in Italy where the care pathway provides continuous psychological support. We cannot exclude a positive effect of psychological treatment on stress management. A major strength of this study is that it is a longitudinal study and it is the first to investigate stress levels and their relation with cross-sex hormonal treatment and attachment.

In few words, the study provides information on HPA dysregulation, perceived stress, and attachment patterns of transsexual patients. Untreated transsexual patients expressed elevated CAR, together with perceived stress and attachment insecurity. The insecure attachment styles (anxious and avoidant) were associated with higher CAR and perceived stress in untreated transsexuals. Finally, there appeared to be a relationship between cross-sex hormone therapy and lower CAR and perceived stress in transsexuals, independently of the attachment style.

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**Conflict of Interest:** The authors report no conflicts of interest.

## Statement of Authorship

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Marco Colizzi; Rosalia Costa; Valeria Pace

#### (c) Analysis and Interpretation of Data

Marco Colizzi

### Category 2

#### (a) Drafting the Article

Marco Colizzi; Rosalia Costa

#### (b) Revising It for Intellectual Content

Marco Colizzi; Rosalia Costa; Valeria Pace; Orlando Todarello

### Category 3

#### (a) Final Approval of the Completed Article

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