Can Gender Differences in Distress Due to Difficult Voices Be Explained by Differences in Relating?

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Abstract

Background Research on gender differences has found that women relate to negative voice hearing experiences with more negative emotions and report more distress due to voices, which may be rooted in differences in relating to voices. This study used a robust methodology and a large sample to explore gender differences in relating to voices and voice distress.

Methods Matched samples of male ($n = 124$) and female ($n = 124$) voice hearers were drawn from a survey for secondary analysis. Voice severity (e.g., frequency or loudness), voice distress, and different types of dysfunctional (i.e., passive or aggressive) and functional (assertive) relating were measured. Group comparisons, mediation models, and network analyses were calculated.

Results Female voice hearers reported more severe voices, more voice distress, more passive, and less assertive relating. Mediation and network analyses yielded evidence for pathways from gender to voice distress via relating and via differences in voice severity.

Conclusion Gender differences in the emotional impact of voices can be partially explained by relating behavior. Psychological interventions for voice hearing could be optimized by exploring the influence of gender in the emergence of distressing voices. Nevertheless, gender differences need to be treated as one of several different possible mechanisms when working with individual patients.

Keywords Relating therapy · Voice hearing · Auditory hallucinations · Schizophrenia · Cognitive behavioral therapy · Interpersonal behavior

Introduction

Hearing distressing voices in the absence of external stimuli has always been an equally fascinating and challenging topic in health care. On a phenomenological level, a recent study on a large sample of voice hearers identified four clusters of voice hearing (McCarthy-Jones et al. 2014). Specifically, these were (1) repetitively speaking commanding and commenting voices, (2) “own thought voices” that speak in the

first-person and vocalize memories/thoughts, (3) “nonverbal voices” vocalizing words that don’t make any sense, and (4) “replay voices” that reiterate a memory of heard speech. Most patients experience voices from multiple clusters, with the commanding and commenting voices being the most prevalent form (86%). Research efforts have long focused on the neural basis of voice hearing in terms of neurofunctional deficits in signal-detection and intentional inhibition (Waters et al. 2012). In recent years, however, the increasing dissemination of cognitive behavioral therapy (CBT) for psychosis and service user guided therapies for voice hearing has also facilitated the exploration of the psycho-social causal factors (e.g., childhood trauma; Daalman et al. 2012) that can precipitate voice hearing and of the individual meaning of the voices in terms of underlying emotional conflicts involving anger, shame, or low self-esteem or in terms of the identity of the voice (Corstens and Longden 2013).

While hearing voices has traditionally been linked mostly to psychotic disorders such as schizophrenia, recent research

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has found voice hearing to be common across many mental disorders (Waters and Fernyhough 2017) and also in the general population (Larøi et al. 2012), with the latter group exhibiting no need for help. In light of these results, contemporary conceptions of clinically relevant hallucinations have been gradually extended to include the impact of voice hearing such as voice related distress as a core element—rather than focusing on the phenomenon of hearing voices in and of itself (Greenwood et al. 2010; Thomas et al. 2014). This lead to the emergence of a new “wave” of symptom-targeted psychological interventions for voice hearing aimed at reducing distress due to hearing voices (e.g., Hayward et al. 2017), reducing the compliance with harmful command hallucinations (e.g., Birchwood et al. 2014), or facilitating mindful disengagement from distressing voices (e.g., Strauss et al. 2015). To further improve on these efforts, we require a deeper understanding of mechanisms that underlie a distressing voice hearing experience and the key variables that facilitate or predict these mechanisms.

Based on the idea that voice hearing bears similarity to relating to other people, etiological research and new approaches to therapy have adopted a relational framework. Research on the relational framework continues to generate evidence linking social schema (Paulik 2012) with functional and dysfunctional relating behavior (Hayward et al. 2020; Sorrell et al. 2010) and the positive or negative impact of voice hearing. Among the therapies based on this framework, cognitive therapy for command hallucinations focuses on the voice hearers’ perception of their voices as superior in social rank and seeks to modify beliefs about the voices’ power and control (Birchwood et al. 2014). At least three other therapies are based on the relating framework and included behavioral elements, either by facilitating a constructive ‘live’ dialogue between the voice hearer and the voice (Voice Dialogue approach; Corstens et al. 2012), by practicing how to respond more assertively to difficult voices in a simulated setting (AVATAR therapy; Craig et al. 2018), or by means of experiential role-plays (Relating therapy; Hayward et al. 2017). With RCT findings providing preliminary evidence on the efficacy of these therapies, the relating framework has become a promising approach to understanding the mechanisms maintaining distress due to voice hearing.

Focusing on functional compared to dysfunctional relating as a core mechanism to explain voice distress, a previous study by Hayward et al. (2016) hypothesized gender to be a key predictor for an increased risk of dysfunctional relating and increased distress due to voice hearing. This hypothesis was based on the premise that relating to voices mirrors relating to others and is consequently affected by the same gender differences that are found in interpersonal behavior. For instance, we may assume that relating to a voice characterized by dominance, intrusiveness and negative content

directed at the voice hearer corresponds closely to a social situation of bullying victimization. Consequently, gender differences found in coping with bullying, such as women showing more avoidance and less assertiveness (Jóhannsdóttir and Ólafsson 2004) should also be found in relating to voices. Adding to this theoretical plausibility, gender differences in voice hearing have repeatedly been found. For example, female participants in general population samples show higher rates of auditory hallucinations (Murphy et al. 2010). When comparing male and female patients with a schizophrenia diagnosis and auditory hallucinations, gender differences were predominantly found in the emotional impact of voice hearing, with female participants reporting more negative feelings of shame, guilt, and anxiety due to voices (Toh et al. 2020). Finally, Hayward et al. (2016) found that female voice hearers prefer more distance when relating to their voices and reported more avoidant behavior and negative emotions due to their voices. In sum, previous research already points to gender differences in voice distress and voice relating, which suggests a possible connection between these variables. To date, however, no study has explored whether differences in relating can explain differences in the impact of negative voices.

In this study, we aimed to replicate previous findings on gender differences in voice distress and relating to voices, utilizing a newly developed questionnaire that assesses typical relating styles when interacting with difficult voices. Furthermore, we hypothesised that female gender would predict increased voice distress due to gender differences in relating to voices.

Methods

Participants

Participants for this study were drawn from a large sample of 402 participants (37.6% female, age: $M=40.47$, $SD=13.40$) recruited from inpatient units and community mental health teams in 14 Mental Health Trusts within the National Health Service (NHS) in England for the validation of a relating to voices questionnaire (Hayward et al. 2020). Inclusion criteria for the initial study were: age of at least 18 years, voice hearing for six months or longer, and sufficient English language skills to complete the questionnaires. For the purpose of the present study, we only included participants from the original sample who reported hearing voices at least once within the week prior to the research assessment.

A subsample was drawn using a pairwise-matching procedure. Pairs of male and female voice hearers were matched according to (1) age (no more than two years of age difference) and (2) education level (equal level of education or one step above/below). Furthermore, participants were

matched (3) by self-reported primary diagnosis if possible (i.e. preferred matching of pairs with the same diagnosis; if no match was possible, participants were matched based on a broader criterion, comparing those with psychotic disorder vs. other diagnosis). This resulted in a sample of 248 participants consisting of 124 matched pairs, with 75% of the participants ($n = 93$ pairs) being matched by primary diagnosis. Demographic and clinical data on the male and female participants included in this study are summarized in Table 1.

Table 1 Demographic and clinical sample characteristics

	Female	Male
N	124	124
Age (M, SD)		
Education level		
No formal qualification	8.87%	6.45%
Secondary/high school qualification	26.61%	27.42%
College/sixth form qualification	17.74%	20.16%
Undergraduate degree	14.52%	12.10%
Postgraduate degree	2.42%	3.23%
Other	4.84%	5.65%
Ethnicity		
White (British)	85.48%	84.68%
White (other)	3.23%	0.81%
Black (British)	1.61%	2.42%
Asian (British)	2.42%	8.06%
Mixed	2.42%	0.81%
Other	4.03%	3.23%
Primary diagnosis		
Psychotic disorder	62.10%	75.81%
Drug induced psychosis	0.00%	2.42%
Borderline personality disorder	13.71%	3.23%
Bipolar disorder	6.45%	4.03%
Depression	6.45%	4.03%
PTSD	3.23%	1.61%
Not stated	8.06%	8.87%
Years with voice hearing (M, SD)	17.74 (13.36)	16.36 (12.84)

Materials

Relating to Voices/Others Questionnaires

The Approve questionnaires were utilized to assess relating to voices and other people. The Approve questionnaires were created in a four stage process involving item generation, item revision following feedback from researchers, clinicians, and people with lived experience of hearing voices, and a final item selection as well as validation based on the same sample as the current study (Hayward et al. 2020). With 2×15 items, the Approve questionnaires measure relating to voices or other people in difficult interactions. Specifically, assertive relating, aggressive relating, and submissive/passive relating are measured with five items each (see Table 2 for the full item list). The Approve Voices questionnaire invites the respondent to consider these items with regard to their “typical” way of relating to voices [“when voices are being difficult (e.g., treating me badly)”], whereas the Approve Social questionnaire assesses the respondent’s typical ways of relating to other people (“when other people are being difficult [...]). Participants were instructed to select the answer that best reflects their typical response to voices or other people on the scale 0 (disagree completely) to 10 (agree completely). Participants were given the option to indicate whether any item was not applicable to them by choosing an “N/A”-option.

Voice Hearing

The severity of voice hearing and the distress due to voice hearing were assessed with the Hamilton Program for Schizophrenia Voices Questionnaire (HPSVQ; Van Lieshout and Goldberg 2007). The HPSVQ is a nine-item measure that assesses the two factors (Kim et al. 2010) pertaining to voice severity (including frequency, loudness, duration, clarity, and compliance with commands) and voice distress (including interference with life, negative voice content, distress, and negative self-appraisal due to voices) as experienced in the preceding week. The HPSVQ-scores have been shown to

Table 2 Item list of the approve voices and social ordered by aggressive, assertive, and passive relating style

When voices/other people are being difficult (e.g., treating me badly), I respond by...		
Aggressive	Assertive	Passive
...Yelling at them	...Repeating my own opinion if they don't listen the first time	...Allowing them to get on top of me
...Shouting and screaming	...Presenting and defending my own view	...Finding myself at their mercy
...Shouting out loud at them	...Hearing what they are saying but also stating my own views	...Giving in
...Swearing at them	...Standing up for myself	...Doing what they want
...Telling them to shut up	...Letting them know that I wish to be left in peace right now	...Telling myself they are right even though I don't believe they are right

correlate highly with clinician-administered interview-based assessments (Kim et al. 2010).

Depression, Anxiety, and Stress

General mental health problems were assessed with the 21-item Depression Anxiety Stress Scales (DASS-21), which provides scores for depression, anxiety, and stress levels in the preceding week. The DASS-21 has been extensively validated and shows high internal consistency, concurrent validity (Antony et al. 1998), and construct validity (Henry and Crawford 2005).

Procedure

Participants who met the inclusion criteria were recruited and informed about the study by clinicians within the participating inpatient units and community mental health teams. For the study, participants were invited to meet with a member of the research team. At the start of this meeting, the participant information sheet was reviewed and any questions about the study were answered. Participants were advised that they could end their participation at any point without giving a reason and without their care being affected. Written informed consent was obtained from all participants.

Next, several measures were completed in line with an assessment protocol (for a more detailed description, see: Hayward et al. 2020). First, participants provided demographic data—including the diagnosis they had received. Next, they started with the first half of the Approve questionnaires (either the Approve Voices or Approve Social), followed by clinical outcome questionnaires including the HPSVQ and the DASS-21. Finally, participants answered the second half of the Approve questionnaire. The Approve questionnaires were split and presented in a random order for the purpose of more conservative testing in the original validation study (Hayward et al. 2020) from which the data for this study was extracted. Following the assessment, participants were able to provide written feedback on the questionnaires.

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by an NHS Research Ethics Committee (reference 18/LO/0046) and the NHS Health Research Authority.

Data Analysis

All data analyses were carried out using R 3.6.1 (R Core Team 2019). In a first step, we compared the mean scores of male and female participants for all variables of interest

(voice severity, voice distress, relating scores, and general mental health parameters) using two sample *t* tests. To account for alpha error inflation, the tests were corrected using the Bonferroni correction for the significance level (i.e. for a global significance level of $\alpha = 0.05$, the threshold for each of the 11 individual *t* tests was $\alpha = 0.0045$). Additionally, Cohen's *d* was calculated for all tests to compare the total size of gender differences on all variables (small effect size: $0.20 \leq d < 0.50$, medium effect size: $0.50 \leq d < 0.80$, large effect size: $d \geq 0.80$). Finally, all of the aforementioned group comparisons were repeated while controlling for diagnosis by calculating linear regression models of the outcome-variables with gender and diagnosis entered as predictors.

Next, we tested the hypothesis that gender differences in voice distress are mediated by relating to voices. We carried out structural equation modeling to calculate separate mediation models for each relating factor that showed significant gender differences. The indirect effect (*ab*) comprising the path from gender to the respective relating factor (*a*) and the path from the relating factor to voice distress (*b*) was tested for significance. Additionally, to double-check whether the hypothesized pathway from gender to relating to voice distress emerges from the data, we performed a network analysis with a graphical lasso (glasso) based optimization of the covariances. A model including gender and all HPSVQ and Approve factors with significant gender differences was initially calculated to explore whether the partial correlation matrix would include pathways between gender and voice distress via relating to voices and whether this was the strongest pathway in terms of correlation size ("Relating to Voices"-network model). Finally, mental health parameters were added in an "Extended Mental Health" network model to explore whether connections between gender and voice distress remained stable when global psychopathology markers were controlled for.

Results

Gender Differences in Relating, Voice Hearing, and Mental Health Parameters

Gender differences in all variables of interest are summarized in Table 3. *T* tests showed significant between-group differences in relating to voices and others. Female voice hearers responded less assertively and more passively to voices. They showed a similar tendency in passive responding to other people. However, this difference was non-significant under the Bonferroni-corrected alpha level. Furthermore, female participants rated their voices to be significantly more distressing, had higher voice severity scores, and showed higher levels of anxiety and stress. All

Table 3 Differences between female and male voice hearers in relating, voice hearing, and mental health

	Means		T test			Effect size		
	Male	Female	T	p	p _{corr}	d	95% CI lower	95% CI upper
Assertive relating to voices	5.53	4.58	−2.97	0.003	0.036	−0.38	−0.63	−0.13
Aggressive relating to voices	4.35	4.48	0.37	0.710	1.000	0.05	−0.20	0.30
Passive relating to voices	4.33	5.56	3.64	0.000	0.004	0.47	0.21	0.72
Assertive relating to others	5.83	5.30	−1.88	0.062	0.682	−0.24	−0.49	0.01
Aggressive relating to others	3.46	3.61	0.53	0.595	1.000	0.07	−0.18	0.32
Passive relating to others	4.19	4.79	1.97	0.050	0.547	0.25	0.00	0.50
Voice distress	8.96	10.95	3.78	<0.001	0.002	0.48	0.23	0.73
Voice severity	11.66	13.66	4.68	<0.001	<0.001	0.59	0.34	0.85
Depression	1.52	1.65	1.14	0.255	1.000	0.15	−0.10	0.39
Anxiety	1.24	1.56	3.43	0.001	0.008	0.44	0.18	0.69
Stress	1.42	1.74	3.40	0.001	0.009	0.43	0.18	0.68

p_{corr} = Bonferroni corrected p-value

results remained unchanged when diagnosis was controlled for—with the sole exception of passive relating to others, for which the uncorrected results became non-significant ($b = 0.488$, $SE = 0.32$, $T = 1.55$, $p_{uncorr} = 0.123$).

Mediation Effect of Relating to Voices on Voice Distress

Based on the differences reported above, we tested whether (1) assertive relating and (2) passive relating to voices mediated the association between gender and voice distress. For assertive relating, no significant indirect effect was found due to a low association between assertive relating and voice distress (Fig. 1, mediation model 1). Passive relating, by contrast, mediated 33.73% of the total effect of gender on voice distress (Fig. 1, mediation model 2).

Exploratory Network Analysis

The initial “relating to voices” network model including the variables of gender, passive relating and assertive relating to voices, voice severity, and voice distress showed no direct connection between gender and voice distress; instead, two separate pathways connected both variables (see Fig. 2, left). One pathway included voice severity, with female gender being associated with higher levels on the voice severity scale, which in turn was associated with increased voice distress. The other pathway included assertive relating to voices, with female gender being associated with decreased levels of assertive relating. Assertive relating, in turn, was negatively correlated with passive relating. Passive relating, finally, was associated with higher levels of voice distress. Lastly, there was a connection between both pathways, with more passive relating being connected with higher voice severity. Notably, while a mediated pathway from gender to

voice hearing via relating was found in this network, partial correlation coefficients connecting gender and relating were somewhat lower than the partial correlation between gender and voice severity.

When global levels of anxiety and stress were added to the network (Fig. 2, “extended mental health network”), no direct connections between gender and voice distress involving any of the newly added parameters emerged. Furthermore, the “voice severity” pathway remained unchanged. However, the “relating” pathway was extended and now included both stress and anxiety as intermediary variables that connected passive relating and voice distress.

Discussion

In this study, we tested whether gender differences in voice hearing experiences can be explained by differences in relating to voices. Our results replicated previous findings that female voice hearers tend to have more severe voice hearing experiences (Murphy et al. 2010), report more negative emotions and distress due to voice hearing (Toh et al. 2020), and tend to relate less functionally (Hayward et al. 2016) when compared to male voice hearers. In general, significant effect sizes were small to medium ($0.37 \leq |d| \leq 0.59$). To translate this range of effect sizes into more understandable terms of overlapping variance (Magnusson 2020): There is an increased chance (i.e., 64.4–72.2%) that a randomly selected female voice hearer shows more distress and less functional relating than a randomly selected male voice hearer. Overall, however, the within gender variances in individual voice hearing experiences still overlap considerably (i.e., 77.2–85.3% overlap). Therefore, while population-wide trends for gender-differences exist, the individual voice hearing experience varies from person to person. In clinical

Fig. 1 Mediation models for assertive and passive relating. Significant effects printed in bold

Mediation model 1 (ASSERTIVE RELATING):

Mediation model 2 (PASSIVE RELATING):

Relating to Voices Network

Extended Mental Health Network

Fig. 2 Network models including gender, passive and assertive relating, voice characteristics, and voice impact (left) as well as stress and anxiety (right). Numbers in between lines denote the partial corre-

lation between the two connected variables controlling for all other variables in the network

practice, the knowledge of the gender differences can help to inform the diagnostic process and lines of inquiry when initially meeting patients. But at the same time, we need to remain curious about individual differences and avoid over-generalization when delivering person-centered therapy.

Of importance, our findings extend previous results by offering some evidence for a pathway from gender to voice distress via increased levels of passive relating. This is in line with the hypothesis that relating differences drive gender differences in voice hearing. Additionally, using network analysis, we found an extended pathway between gender and voice distress via assertive relating and passive relating. This could point towards an interdependence of the relating styles, where the passive reaction to the voice is the result of reduced assertiveness. In sum, these associations between assertive relating, passive relating and distress corroborate the basic tenets of the relating therapy approach that improving assertive relating can help to reduce less functional responses to voices and thereby reduces distress.

Additionally, in order to further refine our underlying assumptions that gender differences in relating to voices correspond to global differences in social relating, a closer inspection of the Approve Voices scales and the Approve Social scales adds helpful information. By descriptive values, women responded less assertively and more passively to both voices and other people. However, effect sizes for social relating (assertive: $d = -0.24$, passive: $d = 0.25$) were notably lower than for relating to voices (assertive: $d = -0.38$, passive: $d = 0.47$), and only relating to voices yielded consistently significant results when accounting for alpha-error inflation. However, a comparison of our effect-sizes to previous studies on gender differences in relating [i.e., responding to bullying with assertiveness: $d = -0.28$, and with avoidance: $d = 0.35$, transformed from R^2 reported in Jóhannsdóttir and Ólafsson (2004)] shows that our effect sizes regarding social relating correspond to previous findings. Conversely, it seems that gender differences in relating to voices constitute an amplification of gender-role conforming differences in social relating. At this point, however, further research is needed to replicate this pattern of results and explore the factors that drive this translation of social relating styles to relating to voices.

Finally, while relating accounted for some of the gender differences in voice distress, network analysis also yielded a pathway that involved gender differences in voice severity. Possibly, women tend to experience more distress due to voices and relate more passively to them because they hear voices more frequently, more loudly, and for longer periods than men. The matching procedure utilized for this study makes it unlikely that this difference can be explained by differences in diagnosis or illness duration (see Table 1) or demographic variables. However, since we have no data on medication or treatment history, we cannot

determine to what extent gender differences in voice severity stem from etiological differences or differences in treatment, e.g. differences in prescription practice (Rothbard et al. 2003), efficacy (Usall et al. 2007), and pharmacodynamics of antipsychotic drugs (Seeman 2004). On a related note, the composition of our sample prevented us from examining the role of gender differences across different cultures. It stands to reason that the aggressive-assertive-passive relating continuum is as likely to be affected by cultural norms and the cross-cultural variation in gender norms as it is by gender. To test this hypothesis, future studies will need to collect more ethnically diverse samples. Furthermore, since our data is cross-sectional, we cannot exclude reverse causal effects of passive relating and distress exacerbating voice severity in the long term. At present, the question of what drives the gender difference in voice severity remains open. To further optimize the fit between client and therapeutic approach, future research needs to explore the working mechanisms of gender differences in voice severity.

Strengths and Limitations

Strengths of this study include the matching of the samples which reduces the chance of biased results. Furthermore, the relatively large sample size can be considered a strength as it allows for the detection of medium and small differences and increases the precision of estimates. A limitation is that diagnoses were self-reported. This could have led to reduced accuracy of diagnostic status, especially since there is evidence that mental health professionals are sometimes reluctant to share the exact diagnosis with their patients (Perkins et al. 2018). Secondly, relating and voice hearing were measured by self-report questionnaires. Possibly, self-reports of affect and behavior lead to an overestimation of gender differences in the direction of gender-role conforming behaviors, especially since there are results from other areas of research that show larger differences in self-reported behavioral tendencies than in objectively assessed behavior (Allen 1995), or instances where self-reported symptom intensity shows the opposite effect when compared to objective parameters (e.g., pain perception vs. physiological parameters; Etherton et al. 2014). Whereas voice severity eludes a truly objective assessment, physiological parameters to quantify voice distress and behavioral assessment of relating could be implemented in future research to further elucidate the extent of gender differences. Finally, the current study focuses on negative voices (i.e., when voices become difficult). As there is some evidence for differences in voice valence (with male voice hearers experiencing more benevolent voices, e.g., Toh et al. 2020), we need to interpret

our findings in a larger context of potential gender differences in voice hearing.

Practical Implications and Future Directions

Our results show that relating to voices and subsequent voice distress is connected to gender. Future studies could extend on these findings and explore to what degree these differences are the result of external causes (e.g. more frequent experience of abuse) and whether non-assertive relating amplifies gender differences in voice severity and distress over time. In terms of practical implications, this research may ultimately inform efforts to optimize CBT and relating therapies. Specifically, potential applications could be (1) scanning for gender-typical differences during case-formulation (2) including gender in individual case models when working with male and female participants (3) acknowledging that gender roles may have impacted negatively on relational aspects of voice hearing (in female patients) and utilizing the topic of gender role conformity when working with beliefs about oneself. Moreover, it may be possible to (4) build on any existing gender-typical resources a patient may bring to therapy. In male participants, this could mean fostering gender-role conforming assertiveness. For female patients, this may include broadening the range from which an assertive response is chosen. Rather than focusing on confrontational assertiveness (i.e., hearing what they are saying but also presenting and defending my own view), an assertive response rooted in mindfulness (e.g., notice the voices, notice your own reaction to it, and allow both of it to be) or even in Acceptance and Commitment Therapy (e.g., notice the voices but make responding a deliberate choice) might be more suitable if a female patient conforms to gender norms in society—especially since some trials have found both of these methods to be more effective in women (Gobin et al. 2019; Katz and Toner 2013). Finally, (5) practical implications of our results could also entail acknowledging that – for reasons yet unknown—women can experience voices more intensely and subsequently have more difficulties relating assertively to them. In sum, this study highlights the importance of including gender differences into our understanding of a relational framework and points to a research topic that could become highly relevant to practical application of voice hearing therapies.

Author Contributions BS, CS, AR, TL, and MH were involved in the design of the study. MH and AR co-ordinated the consultation and the collection of data from participants. BS and XS conducted the statistical analysis. All of the authors were involved in the drafting and refinement of the manuscript.

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Compliance with Ethical Standards

Conflict of Interest Björn Schlier, Xenia Sitara, Clara Strauss, Aikaterini Rammou, Tania M. Lincoln and Mark Hayward declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Animal Rights No animal studies were carried out by the authors for this article.

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