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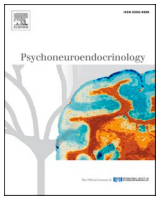

The STRESS-NL database: A resource for human acute stress studies across the Netherlands

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ABSTRACT

Stress initiates a cascade of (neuro)biological, physiological, and behavioral changes, allowing us to respond to a challenging environment. The human response to acute stress can be studied in detail in controlled settings, usually in a laboratory environment. To this end, many studies employ acute stress paradigms to probe stress-related outcomes in healthy and patient populations. Though valuable, these studies in themselves often have relatively limited sample sizes. We established a data-sharing and collaborative interdisciplinary initiative, the STRESS-NL database, which combines (neuro)biological, physiological, and behavioral data across many acute stress studies in order to accelerate our understanding of the human acute stress response in health and disease (www.stressdatabase.eu). Researchers in the stress field from 12 Dutch research groups of 6 Dutch universities created a database to achieve an accurate inventory of (neuro)biological, physiological, and behavioral data from laboratory-based human studies that used acute stress tests. Currently, the STRESS-NL database consists of information on 5529 individual participants (2281 females and 3348 males, age range 6–99 years, mean age 27.7 ± 16 years) stemming from 57 experiments described in 42 independent studies. Studies often did not use the same stress paradigm; outcomes were different and measured at different time points. All studies currently included in the database assessed cortisol levels before, during and after experimental stress, but cortisol measurement will not be a strict requirement for future study inclusion. Here, we report on the creation of the STRESS-NL database and infrastructure to illustrate the potential of accumulating and combining existing data to allow meta-analytical, proof-of-principle analyses. The STRESS-NL database creates a framework that enables

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human stress research to take new avenues in explorative and hypothesis-driven data analyses with high statistical power. Future steps could be to incorporate new studies beyond the borders of the Netherlands; or build similar databases for experimental stress studies in rodents. In our view, there are major scientific benefits in initiating and maintaining such international efforts.

1. Introduction

Stress initiates a cascade of neurochemical and physiological changes that enable an individual to rapidly deal with a stressor and recover thereafter. It is clear that our stress response is extremely complex (de Kloet et al., 2005; Joels and Baram, 2009) and our understanding of stress has its roots in a rich research history stemming from Cannon, Selye, Benard, to McEwen.(Godoy et al., 2018) To adequately respond to acute or chronic stress, an integrated response at the level of emotions, behavior, physiology and (neuro)biology is vital, including temporally distinct changes in brain networks, and stress systems (i.e. the HPA-axis, sympathetic nervous systems, and immune system) (Hermans et al., 2014; Joels et al., 2012; van Leeuwen et al., 2018). The integrated and well-orchestrated stress response is individual-specific, depending on biological and psychological factors, previous experiences, but also the ecological context of an individual's life (Joels and Baram, 2009; Lupien et al., 2009). Stress initiates a cascade of neurochemical and physiological changes which enable an individual to rapidly deal with a stressor and recover thereafter (de Kloet et al., 2005; Ulrich-Lai and Herman, 2009).

The integrated and well-orchestrated stress response is individual-specific, depending on biological (e.g. genetic) and psychological factors, as well as previous experiences. Moreover, it depends on the context of acute stress (e.g. stress type, intensity, controllability) and the ecological context of an individual's life at large (Joels and Baram, 2009; Lupien et al., 2009). Thorough study of the human stress response is of high relevance not only to understand the normal stress response, but also how stress can result in the development of psychiatric and somatic disorders, including depression (Vinkers et al., 2014; Zorn et al., 2017).

Our current understanding of the human stress response stems from a large body of scientific literature based to a great extent on experimental (laboratory-based) acute stress studies in humans, which induce acute stress in a controlled setting using different (versions of) stress-inducing paradigms. This includes the well-known and often-used Trier Social Stress Test (TSST) in individual or group form (Kirschbaum et al., 1993; von Dawans et al., 2011), the Cold Pressor Test (CPT, (Silverthorn and Michael, 2013)) including the socially-evaluated CPT (Schwabe and Schachinger, 2018), the Maastricht Acute Stress Test (Smeets et al., 2012a), but, more recently, also online stress tests (Gunnar et al., 2021), and virtual reality (VR)-based stress tests (Shiban et al., 2016; Zimmer et al., 2019). In these acute stress studies, a physical or socially evaluated challenge is monitored through by outcome measurement, with often salivary cortisol as a biomarker to investigate the HPA-axis (Hellhammer et al., 2009). Studies differ in timing (when are outcomes assessed following acute stress) and correlates (which predictors and outcomes are measured). With regard to timing, cortisol levels are often measured at different time points and time periods following acute stress (Zorn et al., 2017). This is relevant as the stress response has a clear dynamic pattern, with well-known time-dependent effects following stress across (neuro)biological, physiological, endocrine, and behavioral outcomes (Hermans et al., 2014; Vinkers et al., 2013). For example, Schlotz and colleagues showed a strong coupling of the psycho-endocrine response, once an endocrine lag due to the dynamic of the system is considered (Schlotz et al., 2008). With regard to predictors and outcomes, (neuro)biological but also psychological and psychiatric assessments differ from study to study, as do assessments of psychiatric history, current and previous stress and trauma exposure. Importantly, even though exceptions in large cohorts exist, sample sizes of acute stress studies are often limited due to their labor-intensive nature, and this is even more pressing with well-known effects of age, sex, menstrual cycle, and time of day on for example stress-induced cortisol outcomes (Kirschbaum et al., 1999; Kudielka et al., 2004a, 2004b). However, if one wishes to combine data from acute stress studies, it can be very challenging to identify, compare, and combine relevant studies. It is therefore of utmost importance to develop metadata that allow to identify and synthesize data from multiple studies.

To make progress in our understanding of the complexity of the human stress response, collaboration and integration across the field is called for. Therefore, the STRESS-NL database consortium was founded to actively collaborate and capitalize on domain-specific expertise. In this manuscript, we describe the conception and building of the STRESS-NL database, and we present preliminary analyses to demonstrate the content and usability of this collection of acute stress studies. Although currently the database consists only of studies performed in the Netherlands, it can be equally relevant and open for stress researchers from other countries.

2. Materials and methods

2.1. Study identification and selection

The main objective of the STRESS-NL database was to develop a stress database for aggregation, curation and archival of information of most of human acute stress studies in The Netherlands. For an overview of the process how the STRESS-NL database was created, see the research flow chart (Fig. 1; www.stressdatabase.eu). Principal investigators (PIs, the main initiators of the acute stress studies) were identified within the network of the STRESS-NL consortium (www.stress-nl.nl) and invited to participate in this initiative for data sharing of experimental stress studies. PIs were encouraged to share the invitation with other researchers who were potentially interested in the initiative and asked to share data of (un)published research that met prespecified inclusion criteria: i) any type of study design in human subjects (e.g., experimental, longitudinal, cohort, repeated measures); ii) investigating the effects of acute stress in humans with a behavioral intervention (e.g. psychosocial such as a variant of the Trier Social Stress Test; or physical such as the Cold Pressor Test); and iii) at least have measured cortisol concentrations after acute stress per participant. Although this third criterion was required for the current wave of data collection, it won't be required for future waves. Pharmacological intervention studies, for example related to the HPA-axis (e.g. cortisol administrations) were excluded. No exclusion criteria were specified regarding the presence or type of control condition, nor were any limits set on age, gender, diagnosis or any other population characteristics, but all these factors are systematically indicated.

2.2. Data collection and harmonization

Interested PIs were initially contacted for an informal discussion about the eligibility of their data. Eligible PIs were then requested to provide the data in two files: 1) individual anonymized participant data of a selection of variables (gender, age, contraceptive use (where applicable), clinical diagnosis (where applicable), cortisol concentrations) in the PI's preferred format (e.g. excel, SPSS); and 2) meta-information for each study on available data (e.g. questionnaires, cognitive tests, structured interviews, biological outcomes, neuroimaging, and EEG). These two files per experiment were then manually processed and added to the database.

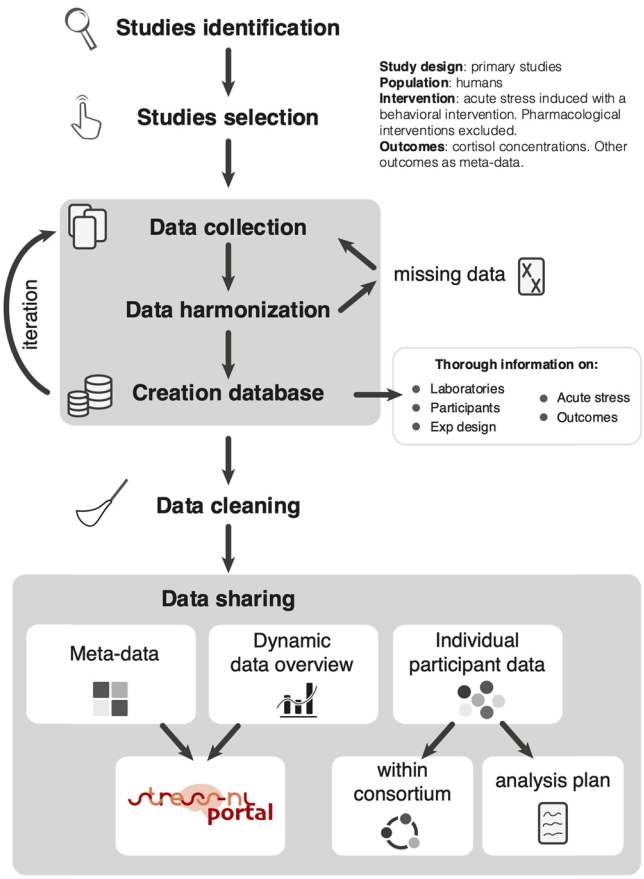

Fig. 1. Overview of the research flow chart of the STRESS-NL database. For details on the contents of the database, see (link). The database can be accessed at three levels:1) meta-data, 2) dynamic data overview (freely available via our web-portal), and 3) individual participant data, which can be accessed only by members of the consortium or via an analysis plan accepted by the consortium. Exp design = experimental design.

In order to integrate data from different studies, data harmonization procedures were set in place. First, we established a naming convention common to all different experiments. For example, we re-calculated the cortisol time points of each experiment so that the baseline value was t = 0 for each experiment. Then, we identified a minimal unique set of variables that could be used to adequately categorize the experiments' meta information. For example, the type of intervention, the concentration/frequency/timing of the cortisol concentration etc. (for a complete list, see Supplementary Table S1). Lastly, we classified particularly heterogeneous variables into subgroups. For example, modifications of the TSST were categorized as "TSST variations". With these steps, we created a stress taxonomy to comprehensively categorize stress research data.

Following data harmonization, a database prototype was created. We focused on four main objectives. 1) The database had a high informational content: information about laboratories, experiments, participants, methods, and various outcomes was accurately and comprehensively represented. 2) The database had to provide intuitive and user-friendly solutions for (meta)data exploration. Variable names therefore were explicit, non-ambiguous, and aligned with customs in the stress field. 3) The database had to be scalable and flexible, with the possibility to accommodate future growth. 4) The database had to comply with the highest ethical standards, and with international, EU, and national law (including European Privacy Protection laws), and provide applications to restrict data access.

A database template was created where experimental studies could be added using an iterative process (Fig. 1). Where necessary, additional information was collected from PIs or from the publications associated with the studies. If information at the individual participant level was missing for continuous variables (e.g. age), we used the group range or, if range was not available, the mean. Data were verified for completeness and consistency. In this first final form, the STRESS-NL database contained two tables, one for the experiments' meta information, and one for the anonymized individual participant data for the limited dataset centered around gender, age, and cortisol values over time.

2.3. Missing data

Despite our intent to be as comprehensive as possible, missing data were encountered for two main reasons. First, we did not perform a systematic search for acute stress studies and PIs contributed data voluntarily. The current version of the STRESS-NL database is therefore not comprehensive of all acute stress studies in the Netherlands. Second, in some studies, missing data was present. In the database, we distinguished between information that was 'not available', for example due to a discrepancy between metadata and individual data, or truly missing, for example due to a technical problem with an assay (e.g. missing cortisol values).

3. Results

The STRESS-NL database collects information of Dutch acute stress studies by categorizing them in the following categories: 1) information about the laboratories (Sections 3.1), 2) characterization of the participants (Sections 3.1), 3) description of the acute stress intervention (Section 3.2) and of 4) the experimental design, and lastly 5) a thorough description of anonymized outcomes (Section 3.3). Furthermore, the database currently contains individual participant data of cortisol concentration after acute stress, although this will not be a strict requirement for data inclusion in the future. We believe that these elements are exhaustive to describe each study; yet, more elements can be easily added in the future if deemed appropriate.

3.1. Database content: meta-study information and participants

In 2021, the STRESS-NL database consists of 12 Dutch laboratories across six different universities, with data from 57 acute stress experiments stemming from 41 independent datasets (Bakvis et al., 2010, 2009; Bouma et al., 2009; Cornelisse et al., 2011; de Brouwer et al., 2011, 2014; de Rooij et al., 2006; Giesbrecht et al., 2007; Hartman et al., 2013; Hermans et al., 2011; Houtepen et al., 2015; Jansen et al., 2016; Kaldewaij et al., 2019; Klumpers et al., 2015; Nelemans et al., 2017; Oei et al., 2006, 2012, 2014, 2018; Quaedflieg et al., 2013a, 2015, 2013b; Roelofs et al., 2009; Smeets, 2010, 2011; Smeets et al., 2012a, 2009a, 2007, 2006a, 2006b, 2006c, 2012b, 2009b; Tollenaar et al., 2009, 2008; Tollenaar and Overgaauw, 2020; van Campen et al., 2015; Vinkers et al., 2013; Vogel et al., 2015; Zhang et al., 2019; Schakel et al., 2020; Tekampe et al., 2021). Supplemental table S2 summarizes the general characteristics of each study included in the database.

The STRESS-NL database contains individual participant information on 5529 participants (Fig. 2a), of which 2281 are females and 3348 males (www.stressdatabase.eu). The age ranged between 6 and 99 years (females: mean[SD] = 29.4[±17.7]; males: mean[SD] = 26.5[±14.8], Fig. 2b). Age had a bimodal distribution, with a clear peak in the early 20's. This overrepresentation of young adults is due to the recruitment strategy of the included studies. 64% of participants were described as healthy individuals, and 16% had confirmed past or current psychiatric or neurological conditions (Fig. 2c). Information about the use of oral contraceptives is available for 61% of women and information about the menstrual cycle for 17% (Fig. 2d).

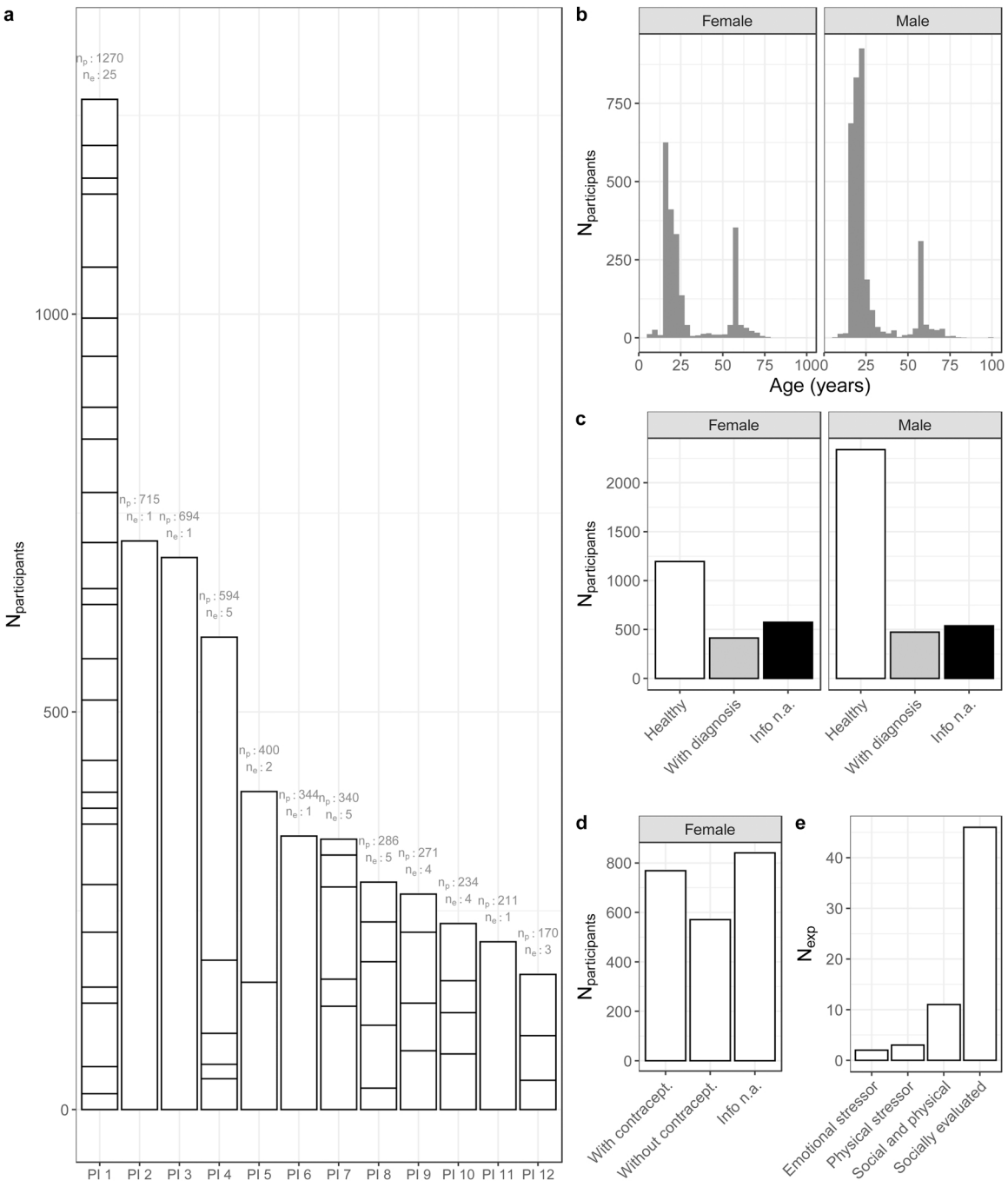

Fig. 2. Demographics, population and intervention. a) Number of participants across laboratories. Each rectangle represents a separate experiment, of height equal to the number of participants, and stacked by principle investigator (PI). n_p: number of participants; n_e = number of experiments. b) Distribution of age across males and females; b) Number of participants based on the presence/absence of a diagnosis. c) Number of female participants (not) using oral contraceptives. d) Number of experiments using different acute stress tests. For a complete list of available acute stress tests, see Suppl table S1. n.a. = not available.

3.2. Type of stress tests

The database includes studies that induced acute stress in humans in a laboratory-setting. Several behavioral paradigms can be used to induce acute stress, which can be roughly categorized by typology (Fig. 2e). Acute stress was induced by social evaluation (i.e., TSST, SECPT, and PST and respective variations, $n_{exp} = 40$; $n_{part} = 4204$), emotional (i.e., aversive movies, $n_{exp} = 2$; $n_{part} = 400$) and physical (i.e., cold pressure test, $n_{exp} = 3$; $n_{part} = 465$) stressors, or a combination of the two (i.e., M-PASAT, P-SECPT, MAST and variations, $n_{exp} = 10$; $n_{part} = 460$). For a list of the available paradigms and their categorizations, see Supplemental table S2. Overall, in 83% of participants in the STRESS-NL database acute stress tests were used, and the remaining 17% of participants were exposed to a non-stressful control condition.

3.3. Available stress-related outcomes

The main (required) outcome of the STRESS-NL database is cortisol concentration, and all studies provided pseudonymized individual participant information for cortisol for all measured time points in the study. All cortisol values belonged to saliva samples. Across studies, between 2 and 11 cortisol timepoints were collected, with a mean of 5,7.

Most of the studies were conducted in the afternoon (58%), with a small percentage in the morning (22,6%) or with a combination of the two (19,4%). Additionally, we collected meta information of several available secondary stress-related outcomes (Fig. 3). These can roughly be categorized in 1) *stress markers*, such as alpha amylase, blood pressure, heart rate, and subjective stress ratings; 2) *questionnaires*, related to general information, such as for childhood trauma, life events, or health status; 3) *genetic outcomes*, such as genome-wide, epigenetic or candidate gene analyses; 4) *cognition/behavioral tests*, such as related to learning and memory, IQ, reward/decision making, attention, emotion, sociality, social anxiety and neuropsychiatric; 5) *brain activity measures*, such as (f) MRI and EEG. The STRESS-NL database contains meta-information on all acquired outcomes, i.e. which tests were performed, what type and quantity of data is available (including questionnaires, subjective stress, physiology, (epi)genetics, and fMRI data). Through our online portal (www.stressdatabase.nl), all outcome information can be found to identify a population of interest. For example, a researcher may be interested in cortisol values after a TSST, but only if information on childhood maltreatment is also available, or search studies that have included fMRI outcomes following stress.

3.4. Cortisol outcomes as an example from the current STRESS-NL database

The STRESS-NL database centrally stores meta-data of all participating studies, but also limited anonymized individual participant data

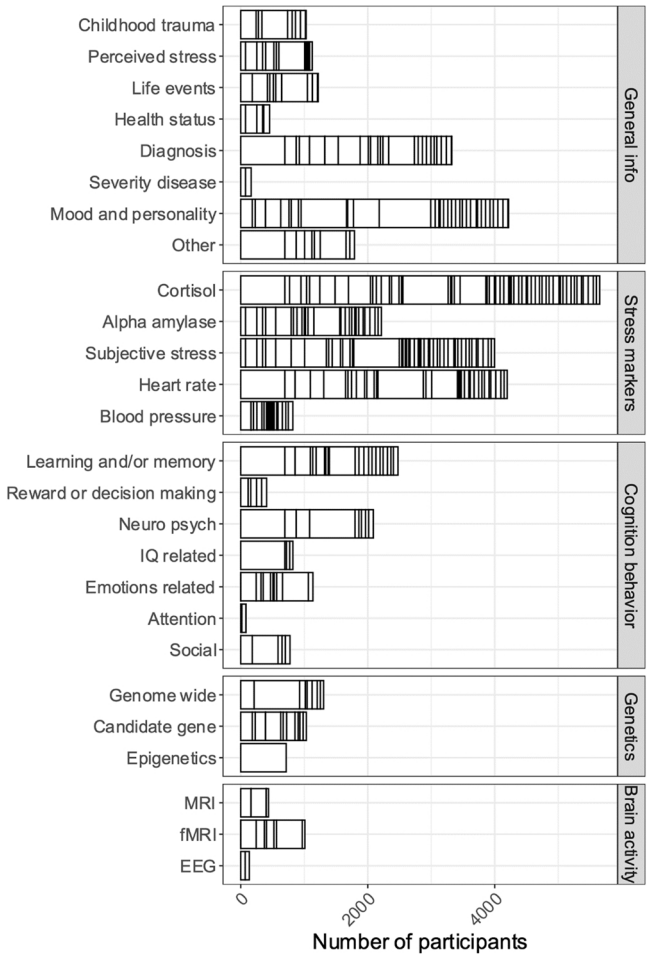

Fig. 3. Overview of participants across outcomes. Number of participants (stress and control groups) for each (grouped) outcome available. Each rectangle forming the frequency bar plots represent a unique study. Of note, all studies have provided individual participant cortisol values.

related to descriptives, such as sex, age, and contraceptive use, and one specific stress outcome, that is, cortisol timepoints and concentrations. In this section, we showcase analyses that can be performed using the STRESS-NL database on human cortisol levels following acute stress. In total, 18 experiments (42%) measured baseline cortisol concentrations (Fig. 4a). No experiment measured cortisol concentration later than 2 h after stress induction (except one study assessing cortisol after 24 h (Cornelisse et al., 2011)), with 85% of cortisol measurements taken within the first hour after stress induction. Since cortisol is dynamically and transiently expressed after acute stress, differences in measured time-points across experiments may highlight biologically relevant heterogeneity.

To illustrate the possibilities of the database, we here calculated the difference between males and females. Across the available data, we selected experiments investigating male as well as female participants, for a total of 23 studies. With the summary statistics of the area-under-the-curve with respect to increase (AUCi relative to baseline) per participant, we calculated Cohen's d, a measure of effect size difference between males and females (Fig. 4b), showing that males generally responded to stress with higher levels of cortisol than females, although there is a high degree of heterogeneity across studies.

At the deepest level of data information, individual participant data enables the full re-analysis of previous experiments. This can be used to confirm existing hypotheses, or test new ones. In Fig. 4c, we selected experiments with at least 10 participants of the following groups: males, females using oral contraceptives, and females not using oral contraceptives. In our database, 4 studies met these criteria. For each participant, we calculated the increase in peak cortisol concentration relative to baseline, with peaks identified for each study independently. Across the identified studies, females using oral contraceptives had a smaller increase in cortisol peak compared to females without oral contraceptives (Fig. 4c). Use of oral contraceptives may therefore partially explain the high variability observed in Fig. 4b – an analysis that would not be possible without the individual participant data.

3.5. Data access and contribution

The STRESS-NL database is governed by a consortium agreement, allowing anonymized individual participant data to be accessed by consortium members. External parties with ownership of human acute stress data can apply to become formal member of the STRESS-NL database, also outside the Netherlands, if they sign and adhere to the consortium agreement. The STRESS-NL database is open for new human acute stress studies, and the consortium agreement is suited and compatible with EU countries. External parties who cannot or do not wish to become member, can gain access to anonymized individual participant data via an analysis plan submitted to the STRESS-NL Steering Committee (there will be a limited fee to maintain and update the database). There, data plans and data release are governed via a consortium agreement with an opt-in principle.

STRESS-NL data can be accessed in multiple ways. Meta-data of individual studies and, in time, summary statistics will be made available via a web portal (www.stressdatabase.eu). Summary statistics can be used, for example, for meta-analyses, Bayesian evidence synthesis, power calculations or the definition of informative priors. Moreover, an analysis plan can be created and submitted to the Steering Committee of the STRESS-NL database. At the website, an interactive user interface is available where researchers can explore experimental design characteristics and their frequencies, and where estimates of the sample size available in the STRESS-NL database are provided. The information of interest is selected and directly transferred to a predefined analysis plan that can then be edited. After central approval, PIs of studies that can and want to contribute to the analysis plan can be approached for the necessary data. This allows direct interaction with the data, without direct contact or storage with identifiable or privacy-sensitive information.

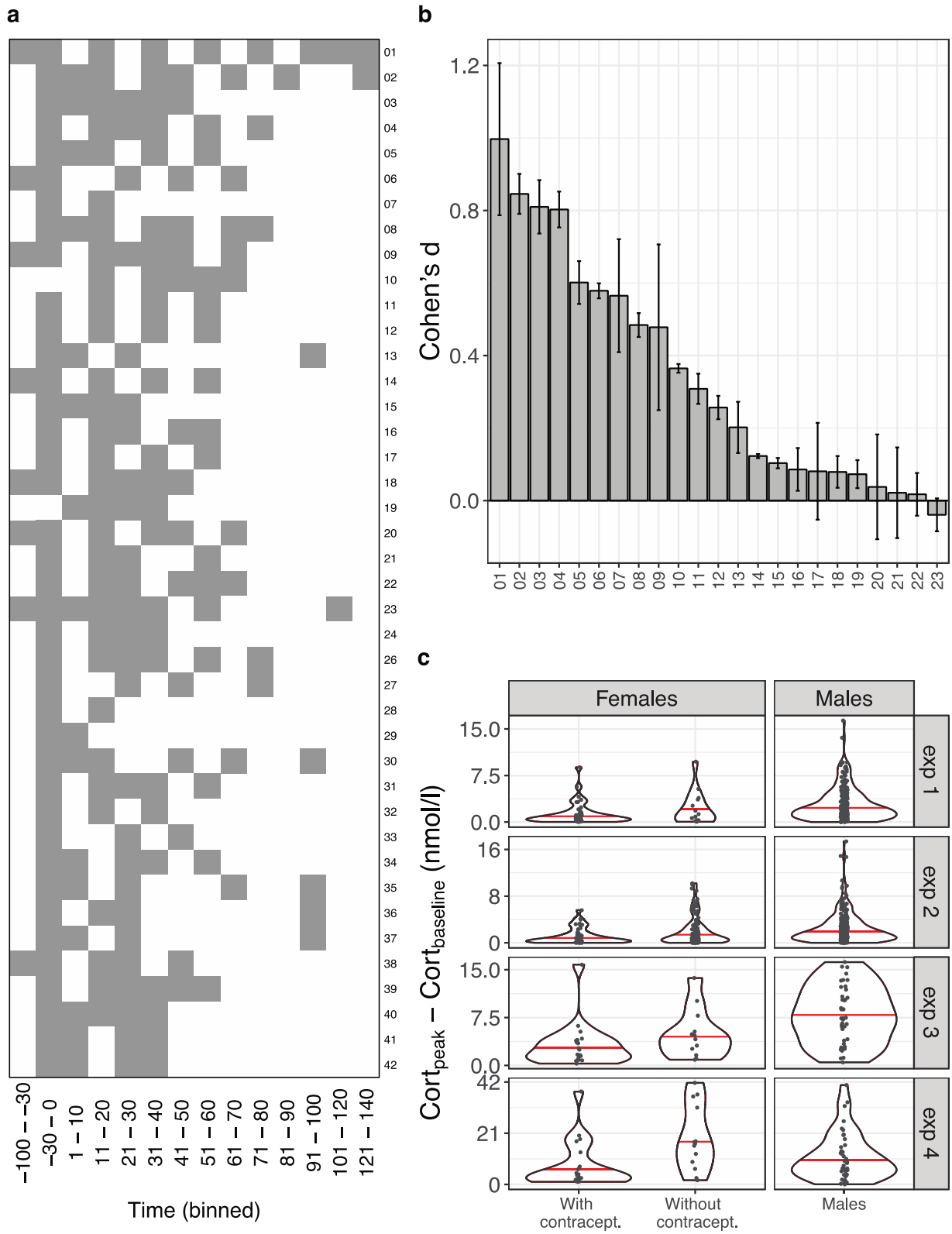

Fig. 4. Examples of analyses for cortisol measurements. a) Heat map of cortisol timepoints across experiments. Grey = measurement present; white = measurement absent. Numbers on the y axis correspond to the experiments in Supplementary Table S2. b) Effect size difference between males and females in cortisol concentration after acute stress measured with the area under the curve (AUCi). Positive effect sizes indicate higher values for males, negative effect sizes for females. The results are shown per study. Numbers on the x axis correspond to the experiments in Supplementary Table S2. c) Difference between peak cortisol and baseline cortisol in studies with males, and females with/without contraceptives. Exp 1 to exp 4 represent the four independent studies in the STRESS-NL database reporting all experimental groups (males, females using contraceptives, females not using contraceptives) in one study, with at least 10 participants per group. Red line corresponds to the median. Each dot corresponds to a participant. Cort = cortisol.

4. Discussion

To promote the reuse and combining of existing data, we established a collaborative interdisciplinary database that combines (neuro)biological, psychological, and behavioral data across many acute stress studies in the Netherlands. Although currently all studies included in the database measured cortisol levels after stress, this will no longer be considered a strict requirement in the future. With 12 Dutch research groups from 6 Dutch universities, we created the STRESS-NL database with information on 5529 individuals (2281 females and 3348 males, age range 6–99 years) stemming from 57 experiments described in 42 independent studies.

This inventory of (neuro)biological, physiological, and behavioral data from laboratory-based human studies employing acute stress tests has the potential to accelerate our understanding of the human acute stress response. The STRESS-NL database contains data that allow meta-analytical as well as proof-of-principle analyses, enabling human stress research to take new avenues in both explorative and hypothesis-driven data analyses with high statistical power (see for example (Harris, 2020)). Such collaboration and combining of studies can lead to novel opportunities for scientific endeavors, for example to disentangle how humans respond to stress in health and disease.

The STRESS-NL database not only facilitates access to existing acute stress data in humans, but also allows a converging consensus on future acute stress studies, for example by harmonizing and summarizing terminology, methodology and data structure across human stress studies. A combined database not only quickly gives insight in the data available nation-wide and whom to contact for data access, but also allows analyses on large sets of data, to validate and replicate previous findings. Data sharing generally increases the sample size and results in a concomitant increase in statistical power, and can lead to more awareness of methodological differences. For instance, one could test hypotheses across populations with a collective large number of participants (e.g. difference between males and females). As stress studies typically have small samples, combining data from different studies also allows for a more optimal analysis of moderating factors that can explain heterogeneity in results. As the database includes various parameters and outputs — from stress markers to genetics and brain imaging to cognitive and behavioral measures and other relevant data — this also enables the integration of stress outcomes at different levels, from physiology, behavior, neuroimaging, to cortisol levels. This may accelerate a 'multi-layer' understanding of stress across relevant outcomes, rather than only focusing on one or two outcome domains.

From our preliminary analyses, it is obvious that quite a large heterogeneity with regard to methodology, population, and outcomes exists. Studies often did not use the same stress paradigm, and outcomes were vastly different and measured at different time points following stress. Moreover, there is currently a distinct bimodal age distribution due to the nature and goals of the studies included so far, which may prevent firm conclusions about age-related changes in stress reactivity. Although this can be regarded a limitation, combining data from multiple studies using different paradigms might offer a better understanding of task-related differences in findings. The next challenge will be analytical: integration of this heterogeneous data requires a thorough and robust analysis plan. Previous research highlighted that simple data aggregation may not always be appropriate for neuroendocrine data (Miller and Plessow, 2013; Miller et al., 2016). Future analyses should be therefore based on state-of-the-art individual participant data methodology (for an overview: https://www.ipdma.co.uk/) or Bayesian evidence synthesis (Kuiper et al., 2012). These methodologies are not limited to performing a statistical test, but they include 1) a thorough assessment of the methodological quality of included studies, 2) an assessment of the risk of bias, 3) a check of the validity of assumptions, 4) they address methodological differences in missing values, time points, assays by accounting for study-specific effects, 5) they use sound statistical models to obtain pooled effects, which can also be used to assess heterogeneity. The flexibility of individual participant data therefore comes with the necessity of increased statistical expertise. Although using percentage change could be at times possible, this can overlook study-specific effects.

So far, details on storage and analysis of outcomes (e.g. method of cortisol assessment such as LIA/RIA, inter- and intra-assay variability, and single or duplicate outcomes) have not been taken into account. To further increase the size and scope of the STRESS-NL database, future steps could be to incorporate new studies beyond the borders of the Netherlands; or build similar databases for experimental stress studies in rodents. In our view, there are major scientific benefits in initiating and maintaining such international efforts.

Role of the funding source

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CRediT authorship contribution statement

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Declarations of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105735.

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