Erschienen in: Nature Ecology & Evolution ; 5 (2021), 3. - S. 311-321
http://doi.org/10.1038/s41559-020-01370-3

Impacts of hypoxic events surpass those of future ocean warming and acidification

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Abstract

Over the past decades, three major challenges to marine life have emerged as consequence of anthropogenic emissions: ocean warming, acidification, and oxygen loss. While the vast majority of experimental research has targeted the former two stressors, the latter remains comparatively neglected. Here, we implemented sequential hierarchical mixed-model meta-analyses (721 control-treatment comparisons) to compare the impacts of oxygen conditions associated with the current and continuously-intensifying hypoxic events (1-3.5 O_2 mgL^{-1}) with those experimentally yielded by ocean warming (+4ºC) and acidification (-0.4 units) conditions based on IPCC projections (RCP8.5) for 2100. In contrast to warming and acidification, hypoxic events elicited consistent negative effects relative to control biological performance, i.e. survival (-33%), abundance (-65%), development (-51%), metabolism (-33%), growth (-24%) and reproduction (-39%), across the taxonomic groups (mollusks, crustaceans, and fish), ontogenetic stages, and climate regions studied. Our findings call for a re-focus of global change experimental studies, integrating oxygen concentration drivers as a key factor of ocean change. Given potential combined effects, multi-stressor designs including gradual and extreme changes are further warranted to fully disclose the future impacts of ocean oxygen loss, warming, and acidification.

The global ocean has been shielding our planet from abrupt climate change, by absorbing a large portion of the anthropogenically emitted carbon dioxide (CO_2) and the excess heat trapped in the atmosphere, leading to ocean acidification (OA, decreasing seawater pH) and warming (OW, rising seawater temperatures)[1]. Additionally, oxygen loss in the ocean (OD, ocean deoxygenation) is being exacerbated by OW and reinforced by geophysical and biochemical processes[2–4]. Referred to as the "deadly trio"[5], these three stressors (OA, OW and OD) are expected to elicit major negative impacts in marine ecosystems over the forthcoming decades[6–8], with consequences for human wellbeing and socio-economic prosperity[9–11]. Should society maintain the current trajectory of greenhouse gases emissions (Representative Concentration Pathway–RCP 8.5), according to the Intergovernmental Panel on Climate Change (IPCC), sea surface pH will decrease by 0.4 units in 2100, temperature will increase by nearly 4ºC, and dissolved oxygen will be reduced in 5%[1,12,13]. In addition to these long-term gradual changes, the frequency, strength, and pervasiveness of abrupt events related to the same three factors will also increase. Hence, extreme acidification events (EAEs), marine heatwaves (MHWs), and hypoxic events (HEs) will become more ubiquitous and potentially more devastating[4,14–17].

The development of adequate adaptation and mitigation strategies to deal with these ocean changes is of utmost importance, and a well-established priority in the international agenda[18]. As such, the scientific community has directed considerable efforts towards investigating the effects of climate change-related drivers on marine biota[19–21]. Since the 2000s there has been a remarkable increase in the number of scientific studies addressing the impacts, and underlying mechanisms, of both OW and OA in a wide variety of marine organisms (Supplementary Figure 1). Research shows that OW disrupts key biological processes, from increased energetic demands to shifts in phenological cycles and distributional ranges, with cascading consequences to ecosystem

functioning[22,23]. On the other hand, OA is known to impact acid-base regulation, energy allocation, and calcification processes of marine organisms by increasing hydrogen ion (H^+) and CO_2 concentrations in body fluids, and altering carbonate saturation state[24,25].

In contrast, oxygen loss has attracted far less attention in the scientific community[2,26] (see Supplementary Figure 1 for comparative publication trends over the last decades). While oxygen loss is known to elicit severely detrimental biological consequences (such as active area avoidance, altered physiology, and high mortality rates, including of marine megafauna)[27–30], its effects have been addressed mainly in the context of acute exposure to hypoxia, in a framework more akin to HEs than to gradual OD. This contrasts with the vast majority of OA and OW experiments, which although short-termed (usually spanning weeks[20,24]), tend to be designed according to the IPCC projections for 2100[1,25]. These distinct approaches greatly increase the uncertainty involved in estimating the full impacts of climate change-related drivers in marine biota. Moreover, very few studies have experimentally investigated the combined action of the "deadly trio", although these three factors will act concurrently in coming years. Factorial experimental designs have been mostly restricted to OA and OW, and tend to report context-dependent interactive (i.e. antagonistic or synergistic) or additive effects[25,31,32], further highlighting the need for further empirical investigation.

Here we integrate existing global change literature and help bridge the knowledge gap around the potential impacts elicited by the looming "deadly trio" on marine life. First, we establish a comparative framework and analyze how distinct biological responses are impacted by the different stressors. Then, as organisms' vulnerability is largely dictated by their inherent physiological contexts, we address how expected responses to stressors can vary across distinct groups in the marine tree of life (fishes, mollusks, and crustaceans), ontogenetic life stages (eggs

and larvae, juveniles, and adults), and the current abiotic conditions to which organisms are adapted and acclimatized (temperate and tropical). Finally, we discuss limitations in current experimental studies and identify potential improvement pathways. The findings should help to redirect research efforts towards a more integrative and realistic view of the impacts of climate change on the marine biota, that would better support decision-making processes for ocean sustainability.

Creating a comparative framework for stressors

To robustly assess differential stressor impacts across taxonomical groups, ontogenetic stages, and climate regions, we identified the main bodies of literature produced over the past decades and retrieved data for stressor magnitudes generally used in climate change studies, integrating the available information on OW and OA, with HEs within a hierarchical mixed-model meta-analyses (HMMM) framework. Thus, considering projections for surface waters in the year 2100 in the most extreme widely used scenario (RCP8.5)[1], OW and OA (as well as OW+OA) were defined by maximum temperature and pH differentials of $\Delta T = +4$ ºC and $\Delta pH = -0.4$ units relative to controls, respectively. We defined HEs based on a fixed interval around ~2 O_2 mgL^{-1} (moderate hypoxia)[17,29,33], and collected experimental data from studies where O_2 concentrations ranging between 1 and 3.5 O_2 mgL^{-1} were used as hypoxia treatment[1,13,28], therefore rejecting extreme hypoxia concentrations (see Methods for detailed discussion on stressor selection criteria).

We retrieved data from a total of 136 papers, corresponding to 721 different control-treatment comparisons, i.e. experiments (see Supplementary Figure 2 for a breakdown of included/excluded studies according to criteria). Data was catalogued according to biological responses, stressor magnitude (hereafter simply referred as “stressor size”), taxonomical group,

species, ontogenetic life stage, and climate region (Supplementary Data 1, see Data Collection in Methods). Using sequential HMMMs (from average to specific responses, cf. Supplementary Tables), we re-analyzed the curated dataset (Supplementary Data 2), and re-calculated effect sizes dependent on stressor size for OW, OA, OW+OA, and HE (corresponding to 4 levels within the factor "Stressor") within the same statistical test, enabling posterior statistical comparisons between these stressors[34,35] (see Statistical Analysis in Methods). Due to a lack of sufficient studies, computing effects sizes for the combined impacts of HE with OA and OW was not feasible (Supplementary Data 1, see Methods). We further stipulated random effects to compute independent, non-correlated effect sizes for the 4 stressors, considering variation within and between papers and experiments (e.g. different experiments performed within each paper).

Using this innovative approach in global change research[36], we calculated independent effect sizes for all stressors (OW, OA, OW+OA, and HE) weighted by stressor size, and measured differential stressor impacts over an array of biological responses (i.e. survival, abundance, energy metabolism, reproduction, and development), and according to: i) taxonomic groups (i.e. fish, mollusk, and crustacean); ii) life stages (i.e. egg/larva, juvenile and adult); and iii) climate regions (i.e. tropical/subtropical and temperate).

Impacts on biological responses

All stressors led to detrimental effects as the average biological response, however HE elicited a stronger effect (-34%) compared to OA (-15%), OW (-16%), and OW + OA (-15%). Moreover, HE consistently inhibited all biological responses, i.e. survival (-33%), abundance (-65%), development (-51%), metabolism (-33%), growth (-24%) and reproduction (-39%) (Supplementary Table 1, Fig. 1). Both the other isolated stressors impacted two of the six

biological responses: OW increased metabolism (+13%) and inhibited survival (-32%); while OA inhibited survival (-8%), and development (-16%). Importantly, while OW+OA also affected three of the six biological responses analyzed (survival by -20%, reproduction by -14%, and development -6%), HE elicited comparatively stronger negative effects in each individual response, except survival where there were no differences between these stressors (see Supplementary Table 1, Fig. 1). Concurrently, HE was the only stressor prompting severe detrimental effects on growth and abundance (i.e. specific taxa density). As such, HE-related impacts consistently impacted cellular (metabolism and reproduction) and individual biological responses (survival, growth, development, and abundance), including fitness-related ones, registering strong effects in two different levels of biological organizations[17].

Impacts across taxonomic groups

From the taxonomic groups studied, we were able to calculate mean effect sizes for fish, mollusks, and crustaceans, which rank amongst the groups most vulnerable to global change[17,25,32,37]. HE was again the most significant inhibitor across the responses studied, as well as the only stressor eliciting significant effects in all combinations analyzed for taxonomic groups over biological responses (Supplementary Table 2, Fig. 2). Averaging all biological responses, aside from HE impacts (-39%, -26%, -40%, for crustaceans, mollusks, and fishes, respectively), OA inhibited responses in mollusks by (22%), while OW and OW+OA also inhibited average responses in mollusks and in fishes (circa -15%). OA effects on survival were restricted to one taxonomical group (crustaceans), whereas OW+OA registered significant effects on the only taxonomical group where estimating effect sizes was possible (crustaceans). OW significantly

impacted the survival of crustaceans and mollusks, but registered no effect on that of fishes, with confidence intervals suggesting fish have highly variable responses to this stressor (Fig. 2).

It was not possible to compute stressor effects on crustacean growth and metabolism due to lack of sample size. However, growth was inhibited by all stressors in fishes, but only by HE in mollusks, while metabolism was stimulated by OW in fishes, and consistently inhibited by HE (in both mollusks and fishes). Thus, OW stimulatory effects on metabolism (Fig. 1 and 2, approx. +25%) did not correlate with positive effects in growth, suggesting that these effects can be classified as adverse, since metabolic costs increased with no positive feedback[7,38]. In general, crustaceans and mollusks appear to be most susceptible to changes in H^+ concentration (which may be linked to calcium carbonate sequestration and damage to exoskeletons and shells[25,39]), whereas fishes are more affected by increases in temperature (possibly due to metabolic costs[40]), or a combination of both drivers[41,42]. Summing up, while effects of OW, OA, and their combination occur only within specific biological contexts, HE impacts are pervasive across the taxonomic (heterotrophic) groups and biological responses analyzed.

Impacts across ontogeny and climatic regions

Gauging the combined biological response from the same heterotroph groups (i.e. fishes, mollusks, and crustaceans) according to their climate regions and ontogenetic life stages yielded, once again, universal HE-induced detrimental effects (mean -40%, Fig. 3; Supplementary Table 3). Concerning ontogenetic life stages, on average and in temperate regions specifically, OW and OW+OA also significantly impacted egg and larval stages, suggesting that the combined effect seems to be mainly driven by OW (around -10% for both). However, these early impacts were not registered for more developed ontogenetic stages (juveniles and adults), where only HE registered

consistent negative impacts across both averaged and specific climate regions (average -35%, Fig. 3, Supplementary Table 3). Interestingly, organisms from tropical regions were shown to be especially susceptible to global change throughout all ontogenetic stages, with HE (-38%), OA (-17%), OW (-28%) and OW+OA (-29%) all prompting inhibitory effects (Fig. 3, Supplementary Table 3). This consistent pattern is potentially linked to physiological thresholds, since unlike temperate inhabitants, animals residing in currently-warmer environments are generally already close to their maximum thermal thresholds (or have a narrower thermal window), which makes them more susceptible to further temperature increases[7,43], especially if coupled with effects from other stressors, such as OA[25,32]. Similarly, the higher vulnerability of earlier life stages (i.e. lower buffering capabilities and physiological tolerance) may explain the detrimental effects of OW+OA and OW on eggs/larvae of temperate animals, and the absence of negative effects on juveniles and adults from this climate region. Thus, while OA, OW, and OW+OA effects on heterotrophs are more specific to tropical regions (and early stages in temperate regions), HE impacts are pervasive across climate regions, and resistance to this stressor does not increase throughout an organism's lifespan.

Perspectives, caveats, and future directions

HE impacts on the performance of marine organisms were greater than those of the other experimentally-tested global change stressors, inhibiting all biological responses analyzed across different categories. Rising temperatures (OW) can markedly shape physiological performance by inhibiting or stimulating biological traits, depending on where the changes start within the organism's physiological thermal window[7,43]. While less pronounced, increases in H^+ concentrations (OA) and reduced carbonate precipitation are linked to altered acid-base regulation

and calcification processes[6,24]. Theoretically, by indirectly provoking shifts in energy allocation, or by directly increasing physiological (e.g. oxidative) stress and lowering thermal/acid-base regulation limits, biological responses elicited by OW and OA could be exacerbated when both stressors co-occur[25,32]. Taking into account higher stressor size magnitudes relatively to isolated treatments (see Supplementary Figure 3 and Supplementary Table 4), in general the combination of OW+OA did not significantly increase effect sizes yielded by isolated stressors, but did produce more pervasive negative effects, e.g. in the reproduction and development of marine animals.

Concurrently, as the majority of animals have a primarily aerobic metabolism, accessibility to species-specific minimum required levels of dissolved O_2 content is critical[28,37]. Indeed, impoverishment of O_2 is known to trigger avoidance behaviour, constraints on thermal ranges and associated biogeography[22], deep physiological modifications, and widespread mortality throughout food webs[16,17,28,44]. Thus, given the fundamental role of O_2 for (esp. higher) life forms in the marine environment, HE causes strong inhibitory effects across all biological responses, taxonomical groups, climate regions, and ontogenetic life stages of marine biota. It is important to note that we do not identify O_2 depletion per se to be more impactful than an "equal" (as a ratio) increase in temperature or H^+ concentration. Here we refer to increasing temperature and decreasing pH corresponding to IPCC projections for 2100, i.e. stressor sizes that are commonly designated as OW and OA, which have been the standard stressor metrics in the climate change research community for the last two decades[19,20,23].

The present meta-analysis identifies oxygen loss (HE) as a major anthropogenic-related stressor, posing a severe and pervasive risk to marine organisms and exceeding the combined effects projected for OW and OA. Our study also points to strong HE impacts on a wide range of biological responses, affecting marine life at different levels of organization, which can be

expected to elicit cascading effects in marine ecosystems with potential socio-economic ramifications[18]. Concordantly, an examination of biodiversity patterns across natural multi-stressor gradients in upwelling systems found that oxygen levels superseded temperature and CO_2 as explanatory factors for macroinvertebrate biodiversity trends in the Eastern Pacific[45]. Thus, given the already-known marked effects on several key ecological and biological features, e.g. identity and density of individual species, life-styles, reproductive success and larval development, feeding modes, and biomass (this study,[3,17,27–29]), HE will potentially elicit major changes in community structure and composition (both in terms of biodiversity and functioning) in future oceans. It is worth noting however, that our analysis included few data on organisms adapted to extremely high levels of oxygen in the ocean (such as polar biota, only 1 study for HE), and organisms from OMZ areas that have evolved to tolerate low O_2 conditions and may persist, if declining oxygen levels do not fall below their critical thresholds.

The prevalence and magnitude of HE impacts demonstrated across traits and taxa indicate that current global change-related research efforts should pay far more attention to the role of oxygen concentration as a stressor. The lack of studies using IPCC projections to address the biological impacts of (average) OD represents an important knowledge gap in climate change research. On the other hand, extreme phenomena, such as HE, MHW, and EAEs have the potential to be even more devastating than their long-term equivalents, as their sudden onset and transient nature deeply limit the potential for acclimation and adaptation of marine biota. Importantly, these phenomena are already taking place and have present-day consequences from both an ecological and a socio-economic standpoint[11,17,46]. With these phenomena expected to become more widespread and to escalate in intensity over the next decades[3,4,33,46], it is of paramount importance to address them under controlled conditions, in order to better understand their consequences and

ramifications. By mimicking and rescaling current-day events, and incorporating regional trends and characteristics, experimental research should be able to provide solid grounds for science-based decision-making and informed risk assessments[10].

Due to insufficient number of papers fitting the criteria, the combined effects of HE with other stressors could not be calculated in the present study. However, it is known that increasing temperature directly and indirectly diminishes O_2 content[13], and that decreasing pH (or elevated CO_2) is also correlated with O_2-poor conditions through organic matter degradation and increased respiration[4,33,37]. For instance in OMZs, where hypoxic waters are usually rich in CO_2 and relatively cold, critical oxygen thresholds of animals tend to be low, thus promoting survival of adapted fauna[47]. More recently, studies focusing on the combined impacts of extreme levels of low O_2 and high CO_2 have found primarily additive negative impacts on marine animals[48–50]. Similarly, large scale changes in temperature and O_2 are reported to jointly lower physiological thresholds in marine biota[37]. In accordance, metabolic-based projections for the future indicate that increasing temperatures and associated decreases in dissolved O_2 content will significantly constrain animal habitat under climate change[51].

Yet, experimental studies on the joint impact of all three stressors on marine fauna are still scarce, leaving a gap for the scientific community to fill. For instance, a rare study assessing the combined OW, OA, and HE impacts on abalone, showed that HE and OA prompted an even stronger narrowing of thermal tolerance range than HE alone[52], suggesting further exacerbation of pairwise-generated negative impacts. Building on the previously mentioned projection models and physiological mechanisms, past records indicate that extreme levels of the deadly trio jointly contributed to mass extinction events, where approximately 95% of all marine species became extinct, e.g. the Great Permian Extinction[53,54]. As such, studies addressing the interplay between

all three elements of the deadly trio in a balanced design, aiming to assess the impacts of gradual, but perhaps more urgently, extreme and sudden changes, represent high-ranking priorities in the field. It is paramount to move towards multi-stressor scenarios (e.g. [36]) that incorporate oxygen depletion, to generate more holistic and accurate predictions of biological responses to the oceans of tomorrow.

Methods

Meta-analysis Design

Defining stressor criteria

Stressor manipulation levels for ocean acidification (OA) and ocean warming (OW) were based on the widely used and well-established projections set by the Intergovernmental Panel on Climate Change (IPCC) for 2100 OA and OW[1]. The "business-as-usual" scenario (RCP8.5) served as reference for these stressors, since: 1) nearly 30 years after the first definition of global change scenarios, greenhouse gas emissions (and consequent climate alterations) are yet to deviate from predictions, and more optimistic scenarios are not backed by current trends[1,55]; 2) a delta pH equal or inferior to -0.4 (which translates to a pCO_2 delta of ~500 ppm), or a temperature delta equal or inferior to +4 ºC (Data S1) represent the most common levels of temperature and pH variation experimentally tested in the last 10-20 years in the climate change research community[11,25].

As for hypoxic events (HE), most O_2 experiments performed have not aimed to compare a concentration delta, and usually target directly measured hypoxia (i.e. low O_2 concentrations) effects per se. Thus, our definition of HE is not given as a delta (as is the case for OW and OA), but rather as a comprehensive range of oxygen concentrations which usually characterize hypoxic events (1 and 3.5 O_2 mgL^{-1}), averaged around what is generally defined as hypoxia in coastal and shelf settings, i.e. ~2 O_2 mgL^{-1} [1,3,13,28,44]. We excluded oxygen treatment concentrations lower than 1 mgL^{-1} (i.e. extreme hypoxic conditions in coastal systems), since these values are often lethal for marine taxa (see Fig. 3 in [27]), or higher than 3.5 mgL^{-1}, which defines limitations for the most active fishes[28]. Simultaneously, suitable controls were inherently defined as being acclimated to > 3.5 mgL^{-1}, to provide a comparable control-treatment response (lowest O_2 concentration used for

control conditions was 5 mgL^{-1}, Data S2). Consequently, species fully adapted to oxygen-poor conditions, e.g. inhabitants of the Eastern Pacific and Indian Ocean oxygen limiting and oxygen minimum zones (sensu [56]), were automatically excluded. A relatively high upper limit for O_2 hypoxic concentrations (3.5 mgL^{-1}) was used[28], yielding conservative results that do not focus on extreme changes in dissolved O_2 levels. To ensure better comparability to other stressor effects, we incorporated an O_2 delta, primarily using explicitly stated control O_2 concentrations within research papers, or retrieving mean oxygen concentrations for the paper's geographic location and year, from datasets made available upon request from the National Ocean and Atmospheric Administration (NOAA) World Ocean Database[57].

In terms of direct stressor comparison, while the most fitting framework would be to likewise estimate O_2 loss impacts using OD projections for 2100 (5-10% loss of O_2 [12,13]), the marked scarcity of experimental data testing very small O_2 differences precludes that approach. It is worth noting that the experimental procedures aiming to emulate OW and OA projections for 2100 (IPCC RCP 8.5) match the conditions of present-day strong/severe marine heatwaves[46] and acidification events[26,58] both in terms of stressor change range (most MHWs average below +4 ºC during their span[46], and EAEs where a 0.4 pH drop is maintained throughout are also infrequent[15,59]) and particularly exposure period (average ~43 days of experimental exposure for OW, OA and OW+OA; Supplementary Data 2). In this context, the rejection of studies featuring extreme hypoxia concentrations further improves stressor comparability. Moreover, given that more extreme levels of OW and OA still occur in nature, we statistically compensated for differences in stressor size manipulations within and among stressors, by incorporating these stressor sizes in the HMMM analyses, and computing effect sizes dependent on the degree of stressor manipulation (see more in Statistical Analysis).

Literature search

Using *Google Scholar* and *ISI Web of Knowledge*, the available literature was scrutinized for experimental/manipulative papers that gauged the effects of global change-related environmental stressors (i.e. warming, ocean acidification, and hypoxia) on biological responses of coastal marine biota (e.g. survival, abundance, energy metabolism, reproduction, development). We used the keywords "warming", "acidification" and "hypoxia", in pairwise combinations, together with "ocean", "sea" or "marine" (e.g. acidification AND warming AND ocean; acidification AND hypoxia AND sea) completing 9 searches. Given the low number of papers yielded for "hypoxia", we performed an additional search, for which keywords included this stressor alone, and the words "ocean", "sea" or "marine" alternately (3 more searches, total of 12). Papers published between 1st January 1990 (roughly marking the emergence of experimental studies directly assessing the effects of global change in marine biota; see Supplementary Figure 1) and 1st March 2016 (end of search) were considered, yielding an initial pool of ~700 papers and ~2000 experiments (Supplementary Data 1).

Not considered were papers where quantitative stressor values were missing (n = 8), controls were not suitable (presence of other confounding factors, e.g. different levels of light, unstable parameters; n = 43), pH was changed using acid addition (n = 6), and any form of data variation (i.e. standard deviation, standard error, confidence intervals or variance; n = 34), or sample size (absence or pseudo-replication; n = 30) was not reported or possible to determine (see Supplementary Data 1). From the initially selected papers and experiments (Supplementary Data 1), inclusion/exclusion criteria yielded a total of 136 papers, corresponding to 721 different control-treatment comparisons, i.e. experiments (Supplementary Data 2)[32,39–42,58,60-190]. For a

detailed description of the number of papers removed at each step of the process, please see the flow diagram elaborated following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Figure 2), and Supplementary Data 1 for the specific rejection criteria used case-by-case. We took into consideration the PRISMA checklist for meta-analysis and review papers/experiments to ensure the best practice in reporting meta-analyses[191].

Data collection

Data points, error estimates and sample sizes were retrieved from tables or calculated from figures using freely available graphical software (Im2graph, v1.20). Error estimates in papers (variance, standard deviation, 95% confidence intervals, or standard errors), were transformed to standard error prior to inclusion in meta-analysis, through appropriate mathematical formulas using sample sizes and means. Whenever the nature of error estimates was unreported, either on the manuscript or supplemental data, we searched online on data repositories for said information (e.g. OA-ICC, PANGAEA). When valid information about the nature of error was still not retrieved, the paper would be removed from analysis, according to the aforementioned rejection criteria (variation not reported/could not calculate response ratio). In cases where control treatments showed no variance (e.g. some experiments report 100% survival under control conditions), we used the variance reported in the stressor treatment for controls as well, to make calculations possible and conservative. If data were presented as log-transformed, we performed a reverse transformation (i.e. antilog) before definite inclusion in the dataset.

The low number of papers that assessed combined stressor impacts HE+OA (n = 1) and HE+OW (n = 2) (see Supplementary Data 1), precluded the calculation of effect sizes for these

interactions, and thus only the interaction OW+OA was considered for HMMMs analyses. When multiple levels of a stressor (e.g. OW) were tested and described in a paper/experiment, only the closest to the designated maximum delta (e.g. $\Delta T = +4$ ºC) was taken as the treatment level. In multispecies papers/experiments (e.g. multiple species in the same mesocosm), responses from distinct species were collected separately, even though their responses were not completely independent. Here we followed the reasoning of previous meta-analyses papers, which state that non-independent indirect effects of acidification, warming and hypoxia such as species interactions are relevant to future scenarios of climate (or global) change, where species will be impacted by both direct and indirect effects[8,24,25]. Moreover, this issue was also addressed statistically by the introduction of random effects in the meta-analysis models (see below).

Data on different biological responses to stressors were collected, including: survival, abundance, metabolism, growth, development, reproduction, behaviour, bleaching, calcification, and enzymatic rates. In papers/experiments where the same biological response was gauged several times through different metrics (e.g. growth measured as changes in biomass, length, and width), only the most biologically inclusive metric was considered (e.g. biomass instead of length for estimating growth) to avoid pseudo replication[25,34]. As such, survival was typically reported as the percentage or number of individuals alive, at the end of the experiment. Papers assessing abundance responses were more common in the field, and were defined as the number of individuals (including number of newly settled individuals). Metabolism was primarily taken as changes in metabolic measurements, such as aerobic scope or maximum metabolic rates. Development was mainly assessed through number of individuals successfully developing over ontogenetic stages. Reproduction was measured through number of eggs produced, or quantification of sexual hormones. Changes in behavioral processes (behavior), number of

393 *Symbiodinium* cells (bleaching), calcium carbonate concentration (calcification), stress-driven
394 changes in antioxidant enzymes (enzymatic rates) and photosynthetic rates (photosynthesis) were
395 also registered. Biological responses with fewer than three data points (n = 3), were not isolated
396 for analyses. Thus, after a first general analysis (Supplementary Table 1), we trimmed responses
397 to include only those with sufficient data to calculate related impacts (e.g. survival, abundance,
398 metabolism, growth, development, and reproduction; Fig. 1).
399 Data were organized by three stressors and one stressor combination (i.e. 4 stressor levels),
400 namely: Hypoxia (HE); Ocean Warming (OW), Ocean Acidification (OA), and combined Ocean
401 Warming + Ocean Acidification (OW+OA). Beyond biological responses, we hierarchically
402 subdivided data into subsets within: i) taxonomical groups (Fish, Mollusk, Crustacean,
403 Echinoderm, and Coral), from which Fish, Mollusk, Crustacean were considered as the main
404 taxonomical representatives of heterotrophs; ii) climate region where the organisms reside
405 (Temperate or Tropical/Subtropical); iii) and ontogenetic life stage (Egg/Larva, Juvenile, and
406 Adult).
407
408 Statistical Analyses
409
410 *Hierarchical mixed-effects models*
411 Meta-analyses were performed on R software[192], using the function *rma.mv* (Meta-
412 Analysis via Multivariate/Multilevel Linear Mixed-Effects Models) available in the *metafor*
413 package[193,194] (see Supplementary Code 1 for the R Script used). First, to calculate effect size and
414 variance estimates for each of the control-treatment comparisons, we used the function *escalc*,
415 introducing:

dat = escalc(m1i = M_T, sd1i = SD_T, n1i = N_T, m2i = M_C, sd2i = SD_C, n2i = N_C, measure = "ROM", data = DataS2, append = TRUE) (see Data S3 for more examples)

"ROM" calculates the ln-transformed response ratio (lnR)[35] between controls and treatment, as lnR = ln (M_T/M_C), while variance for each comparison is calculated as: variance = $SD\_T^2/(N\_T * M\_T^2) + SD\_C^2/(N\_C * M\_C^2)$. After, we fitted the meta-analytic multivariate hierarchical mixed-effects models (see Data S3 for more examples), using the function *rma.mv*:

model = rma.mv (lnR, variance, method = "REML", test = "t", random = list (~ Stressor | Experiment, ~Paper | Experiment), struct = "UN", mods =~ lnSR : Stressor-1, data = dat).

The inclusion of "-1" for the categorical moderator (Stressor) calculates estimates for each of the levels within said moderator, contrasted with a dummy variable zero (i.e. directly testing the null hypothesis), instead of using one of the moderator levels as a reference baseline. Only the interaction term between moderators was used since models with this structure consistently reported the lowest AIC and BIC values. We included a second moderator, the natural logarithm of the difference between control and treatment levels for each experiment (written as "lnSR", Supplementary Data 2 and Supplementary Code 1), interacting with the Stressor moderator (calculated as lnR), to take into account stressor manipulation levels and proportionally calculate effect sizes. For HE, we calculated stressor size as the natural logarithm of the ratio between O_2 concentrations at the control and treatment conditions. For OA, since pH is already a logarithmic scale, we transformed to the natural logarithm and retained the difference between control and

treatment pH levels. Since temperature scaling is highly variable, we used 2º C, i.e. the absolute value corresponding to the freezing point of seawater (-2º C) as a reference baseline, and computed the ratio between control and treatment (e.g. +4 ºC) conditions. Stressor size values for OW + OA treatment were obtained by summing the respective ratios of OW and OA. We used generalized linear mixed modelling with a similar structure to the HMM, to describe the relationship between stressor size and effect size (see Supplementary Figure 3 and Supplementary Table 4). Models were posteriorly validated, by checking for normality in residuals, homogeneity of variances, homoscedasticity, and leverage (Supplementary Code 1). All stressor size values are available in Supplementary Data 2 (lnSR).

We included 2 random effects, "Stressor|Experiment" and "Paper|Experiment", to independently calculate intercepts and slopes within levels, minimizing (multi)collinearity, e.g. in experiments from the same paper, and experiments several stressors were measured. We extended independency within models as much as possible, by using structures that maximized heterogeneity calculation, allowing for level-specific (instead of estimating one value for all levels), independent computation of effect sizes and correlations values, between and within the levels of the inner and outer components of both random effects (see more in [194] and https://cran.r-project.org/web/packages/metafor/metafor.pdf). Thus, we attempted to model data starting from the highest complexity structure, and gradually decreased according to the following order (according to *rma.mv* and *metafor* documentation): unstructured variance-covariance matrix ("UN"), heteroscedastic compound symmetry ("HCS"), diagonal matrix ("DIAG"), compound symmetry ("CS"), and scaled identity-matrix ("ID"). Initially, we began with a completely unstructured variance/co-variance matrix where all parameters were calculated case-by-case ("UN"), to a structure ("ID") where within and between-level correlation coefficients were set to

462 0 (see more in [194]). The majority of our models were run with either a "UN" or a "HCS" structure
463 (Supplementary Code 1), thus entailing high independency between stressors, papers, and
464 experiments.

465 Lastly, to verify significance of effect sizes and confidence intervals calculated using
466 restricted maximum likelihood, instead of using the default z-statistic (*k* degrees of freedom), we
467 performed t-tests. Since t-statistics resort to a t-distribution with a $k-p$ degrees (where p is the total
468 number of model coefficients), they provide more conservative results for small sample sizes, i.e.
469 larger standard errors are computed to deal with uncertainty[194,195].

470

471 *Testing differential stressor impacts and analyzed sub-datasets*

472 Use of the same HMMM to calculate effect sizes and 95% CI estimates for each level
473 within a moderator, enabled us to find significant differences between levels (e.g. H vs OA), in a
474 pairwise post hoc analysis[34,196]. To formally test for differences among levels of each moderator
475 within the mixed model, we applied Tukey's honest significance tests (package *multcomp*) using
476 general linear hypotheses (command *ghlt*), and creating a contrast matrix between all stressor
477 levels using *contrMat* (see Supplementary Code 1).

478 In a step by step approach, and always incorporating Stressor Size as an interactive
479 moderator, we undertook a hierarchical approach, performing several sequential mixed effects
480 models to test the effect of moderators, i.e. variables with potential to influence the response of
481 marine biota to stressor impact (i.e. distinct stressors, response variable, taxonomical groups,
482 climate region, and life stage). We firstly assessed the mean effect of each stressor (i.e. HE, OW,
483 OA, and OW+OA, irrespective of biological responses (including behaviour, bleaching, and
484 calcification) (Supplementary Table 1). We then created subsets of those data, and individual

models were computed assessing the effect of stressors for each biological response (Fig. 1). Within those subsets, we further analyzed differences in stressor impacts within the three most significant animal taxonomic groups (Fig. 2, Supplementary Table 2). Lastly, after taking the negative symmetric value for metabolism and feeding (to prevent counter-directional effect sizes), a final analysis was performed which gauged stressor effects on these three taxonomic groups, according to ontogenetic life stage and climate region (Fig.3, Supplementary Table 3). Please see Supplementary Tables for model results summarized according to estimates for each stressor, and Supplementary Code 1 for full model structures and results, as well as (sub-)datasets used (Supplementary Data 2 as well).

After concluding analyses, lnR and 95% CI estimates were back transformed to R[34]. We used the antilog (i.e. exponential function) to remove the natural logarithm, and allow for a better biological interpretation of the yielded results[34,35]. R is interpreted similarly to lnR, except that the reference value (where control = treatment) to which R is (non-)significant is 1. Therefore, values where $R > 1$ show a stimulation of the variable, while $R < 1$ represents an inhibition of the variable.

Publication bias

To assess the robustness of observed effects, we carried out several analyses to detect: (i) the observable presence of bias (observation of funnel plots), (ii) artifacts stemming from unseen bias (Rosenthal's fail-safe number), and (iii) how much impact a potential bias could have (Duval and Tweedie's Trim and Fill)[34]. The Rosenthal's fail-safe number (N_{fs}) determines the number of effect sizes with no significant effect that are needed to change the significance (*p* value) reported by the model. Defined as $5n + 10$ (where n was the number of experiments), the N_{fs} was above the threshold in all cases reported. Importantly, all Trim and Fill operations that reported a correction

of mean estimates and CI's, did so by increasing the magnitude of the effect. Given that CI's of the main analysis and the Trim and Fill analysis still overlapped, we opted to report the results from the main analysis, which were therefore more conservative (see Supplementary Code 1 for case-by-case differences).

Sensitivity analyses

Using forest plots, the disproportionate contribution of an experiment with a large magnitude effect size to a specific result was assessed by ranking each individual experiment by the magnitude of its effect size, followed by a one-at-a-time removal of the experiments with the largest magnitude effect sizes and re-running the analyzes (Supplementary Code 1). If the exclusion of a specific experiment changed the significance of the overall mean effect size or the heterogeneity statistic, these analyses would be re-run excluding that specific experiment. The same rationale was applied at a paper level, i.e. papers contributing more than 5 experiments were removed, and the analysis was re-run to determine if statistical significance was changed due to that particular paper. Lastly, as we took several datapoints from one paper, e.g. biological responses such as survival and metabolism, we performed an extra-step to minimize non-independence issues in the hierarchical mixed effects approach, and checked for paper bias on the amount of experiments retrieved. To the lowest hierarchical level possible (i.e. when number of papers = 3), all analysis were re-calculated with a single effect size for each stressor per paper, which was calculated via a mixed-effects model as the weighted mean effect size of all combined experiments (e.g. different biological responses) from that paper[34] (Supplementary Code 1).

Data and materials availability

All data and code relating to this manuscript are available in Supplementary Data and Code files.

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Funding

This work was supported by the Portuguese Foundation for Science and Technology (FCT), through the strategic project granted to MARE strategic project (UID/MAR/04292/2019), the PhD grants attributed to ES (SFRH/BD/131771/2017) and CS (SRFH/SFRH/BD/117890/2016), VF (CEECIND/02484/2018), and the DFG Centre of Excellence 2117 "Centre for the Advanced Study of Collective Behaviour" (ID: 422037984). LAL was supported by NSF OCE1829623 and NOAA CHRP award NA18NOS4780172. HOP was supported by PACES program of the AWI and the DFG (German Research Council (Po 278 16-1 und -2) Research group Tersane.

Author contributions

ES, IR, and RR conceptualized the study. ES, IR, and CS collected the data. ES and VF performed the statistical analyses. IR and CS designed the figures. H-OP, CMD, and LL supervised work preparation. ES, IR, CS, VF, H-OP, CMD, LL, and RR interpreted data, and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Figure legends

Fig. 1. Average and detailed (survival, abundance, energy metabolism, reproduction, and development) biological responses of marine biota (combined fish, mollusk, crustacean, echinoderm, and coral) to global change stressors (HE – Hypoxic events, OA – ocean acidification, OW – ocean warming, OW+OA – ocean warming + ocean acidification), taking into account distinct stressor manipulation levels (stressor size). R portrays effect size (response ratio) and 95% CI. The dashed line (R=1) indicates no effect, while R>1 indicates stimulation, and R<1 indicates inhibition. Asterisks indicate significant effect sizes (HMMMs, 95% CI does not overlap R=1), different letters show significant differences among stressors (Tukey HSD tests, $p < 0.05$), and numbers indicate sample sizes (i.e. number of experiments) for each effect size. Statistical outputs are available in Supplementary Table 1.

Fig. 2. Average (all biological responses) and detailed (survival, metabolism, and growth) responses of the main heterotrophic taxonomic groups (crustaceans, mollusks, and fish) to global change stressors (HE, OA, OW, and OW+OA), taking into account stressor size levels. Asterisks indicate significant effect sizes (HMMMs, 95% CI does not overlap R=1), different letters show significant differences among stressors (Tukey HSD tests, $p < 0.05$), and numbers indicate sample sizes (i.e. number of experiments) for each effect size. Statistical outputs are available in Supplementary Table 2.

Fig. 3. Average (all biological responses) response across ontogenetic life stages (egg/larva, juvenile, and adult) and/or climate region (temperate and subtropical/tropical) of the main taxonomic groups (combining crustaceans, mollusks and fish) to global change stressors (HE, OA, OW, and OW+OA), taking into account stressor size levels. Asterisks indicate significant effect sizes (HMMMs, 95% CI does not overlap R=1), different letters show significant differences among stressors (Tukey HSD tests, $p < 0.05$), and numbers indicate sample sizes (i.e. number of experiments) for each effect size. Statistical outputs available in Supplementary Table 3.