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Opinion

Global Warming, Climate Change, and Environmental Pollution: Recipe for a Multifactorial Stress Combination Disaster

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Global warming, climate change, and environmental pollution present plants with unique combinations of different abiotic and biotic stresses. Although much is known about how plants acclimate to each of these individual stresses, little is known about how they respond to a combination of many of these stress factors occurring together, namely a multifactorial stress combination. Recent studies revealed that increasing the number of different co-occurring multifactorial stress factors causes a severe decline in plant growth and survival, as well as in the microbiome biodiversity that plants depend upon. This effect should serve as a dire warning to our society and prompt us to decisively act to reduce pollutants, fight global warming, and augment the tolerance of crops to multifactorial stress combinations.

Highlights

A multifactorial stress combination occurs when more than two to three abiotic and/or biotic stress factors simultaneously impact a plant.

Global warming, climate change, and industrial pollution could result in an increase in the frequency, complexity, and intensity of multifactorial stress combinations impacting plants, soils, and microbial communities.

With the increase in the number of factors simultaneously impacting plants, the survival and growth of plants declines, even if the levels of each of these individual stresses is very low.

The response of plants to a multifactorial stress combination is unique and involves many transcripts and genes that are not altered in response to each of the different stresses applied individually.

The harmful effects of a multifactorial stress combination on the survival and growth of plants, different soil properties, and diversity of microbial communities should serve as a dire warning to our society and prompt us to act drastically to reduce the different sources of multifactorial stresses in our environment.

The Diminishing Resources and Deteriorating Environmental Conditions on Our Planet

The accumulated impact of human life on our planet over the past several decades, and in particular the industrial revolution, resulted in a constant increase in greenhouse gas production (mainly CO_2) caused by the burning of fossil fuels (Figure 1A; www.ipcc.ch/) [1–9]. The accumulation of CO_2 in the atmosphere traps the IR radiation emitted from the surface of the Earth following absorption of sunlight and heats our planet, driving an alarming trend of continual increase in global surface and ocean temperatures, termed global warming (Figure 1A; www.ipcc.ch/, https://ourworldindata.org/owid-grapher, www.eea.europa.eu/) [1–9]. Global warming in turn drives a drastic change in our climate, termed climate change, that is accompanied by an increase in the frequency and intensity of droughts and heat waves (Figure 1B), as well as of other abiotic stress conditions such as flooding, salinity, and freezing stresses (www.ipcc.ch/, www.ncdc.noaa.gov/, https://ourworldindata.org/owid-grapher, www.eea.europa.eu/, www.epa.gov/) [1–9]. At the same time, the overall growth in the global population, coupled with the expansion in residential and commercial land use, is driving a continual decline in the availability of prime agricultural land (Figure 1C; https://ourworldindata.org/owid-grapher) [10–12]. The loss of arable farmland necessitates a continued increase in yield produced from each acre of the remaining land to feed an ever-growing population [7,12,13]. However, the availability of freshwater for use in agriculture is also declining due to the overall population growth and the increase in freshwater demand for residential and commercial use (Figure 1D; https://ourworldindata.org/owid-grapher, www.ipcc.ch/) [1,7,12,13]. As a result, the quality of water used to irrigate crops (e.g., its pH, salinity levels, and content of different contaminants) is declining [7,12,13].

In addition to the gradual increase in day and night temperatures [14–16], the reduced availability and quality of water used to irrigate crops [7,12,13], and the increase in frequency and intensity of

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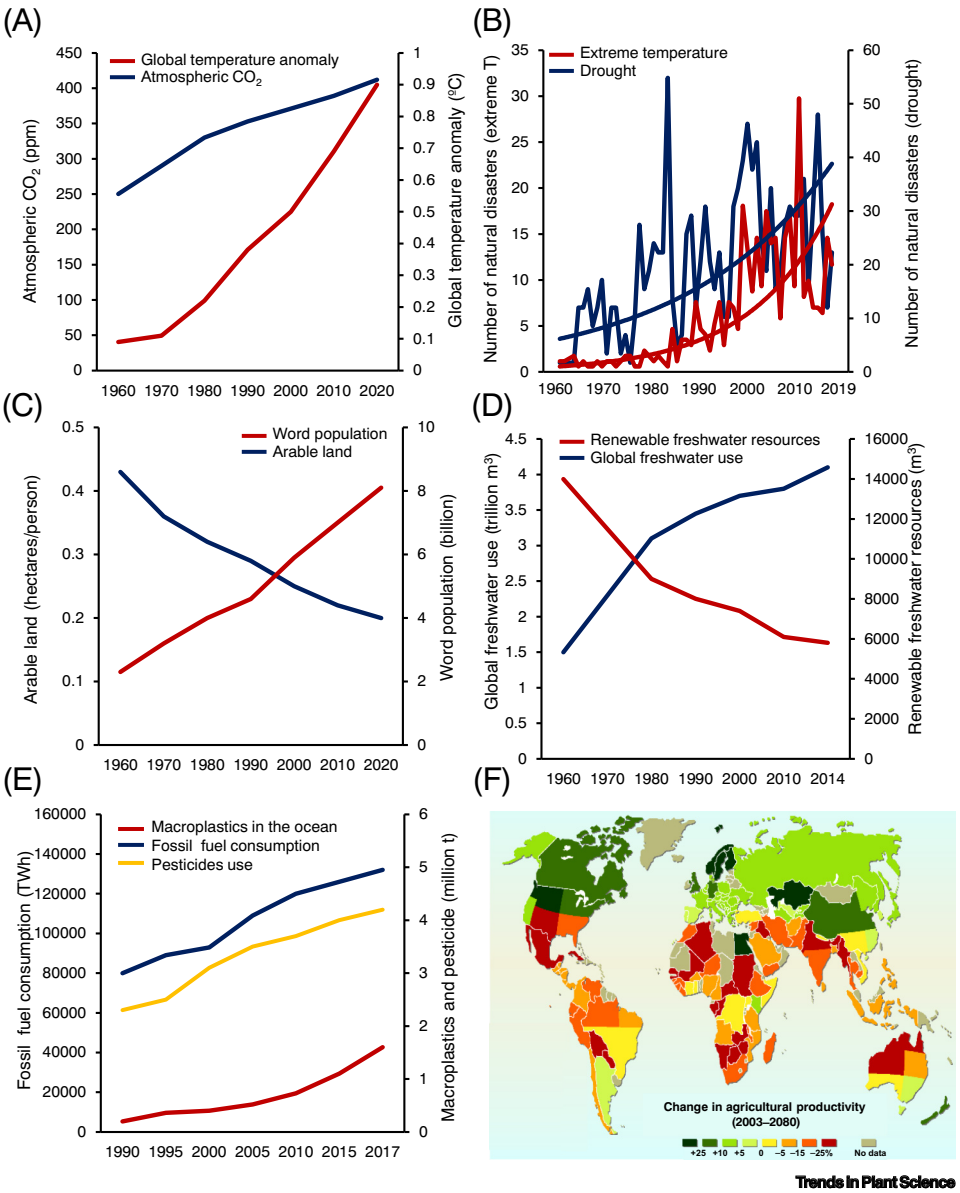

Figure 1. Diminishing Resources and Deteriorating Environmental Conditions Are Drivers of Multifactorial Stress Combination. (A) Global changes in atmospheric CO_2 concentrations and temperature. (B) Global frequency of droughts and extreme temperature episodes. (C) Changes in world population and the availability of arable agricultural land. (D) Global freshwater use and availability of freshwater resources. (E) Global increases in ocean macroplastics, fossil fuels consumption and pesticide use. (F) Predicted changes in global agricultural productivity from 2003 to 2080 as a result of the different processes outlined in (A–E). Data were obtained from www.ipcc.ch/, https://ourworldindata.org/owid-grapher, www.ncdc.noaa.gov/, www.eea.europa.eu/, www.epa.gov/ (as well as other sources outlined in Table S1 in the supplemental information online). Global temperature anomaly is defined as the departure from a reference value (average temperature of the late 19th century, from 1850–1900; Table S1). Abbreviation: TWh, terawatt-hour.

different episodes of abiotic stress, caused by global warming and climate change (Figure 1A,B, D; www.ipcc.ch/, https://ourworldindata.org/owid-grapher) [1–9], plants are subjected to a gradual increase in the concentrations of many man-made contaminants, as well as of different environmental and industrial pollutants (Figure 1E; www.ipcc.ch/, https://ourworldindata.org/owid-

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grapher) [17–20]. These byproducts of human activity include, among others, heavy metals, microplastics, pesticides, herbicides, antibiotics, persistent organic pollutants, tropospheric ozone, and diesel and burn particles. Many of these contaminants can further cause changes in soil pH and salinity levels, as well as damage the stratospheric ozone layer and enhance the levels of UV radiation reaching the Earth surface [17–21]. In addition to directly impacting plant growth and reproduction within many eco- and agricultural systems, many of the environmental conditions described in the previous text were also found to increase the vulnerability of plants to attack by different pathogens and pests, as well as to alter the behavior of different insects, resulting in a decline in many forest ecosystems as well as insect-driven pollination [22–26]. According to computer models, further increases in the frequency and intensity of different episodes of abiotic stress, such as droughts, heat waves, cold snaps, and flooding, are to be expected as global average temperatures increase (www.ipcc.ch/) (e.g., [1–3]). Such increases would further threaten global food production and security, potentially destabilizing different areas on our planet, leading to unrest, hunger, and even wars [27–29]. In addition, the geographical growth areas of many important crops are expected to shift as temperatures climb and conditions worsen (Figure 1F) (www.eea.europa.eu/) [7,8,12].

Although not expected to impact plants all at once, different combinations of the environmental factors, stressors, pollutants, pathogens, and pests, as described in the previous text, are likely to affect plants, crops, and trees growing in different areas of our planet. Furthermore, owing to the continual increase in many of the processes that drive these factors (Figure 1A–E) (www.ipcc.ch/), the likelihood that plants will be subjected to a multifactorial stress combination (Box 1) of several co-occurring stressors is gradually increasing [30,31].

The Impact of a Multifactorial Stress Combination on Plants, Soil, and Microbial Populations

At least two recent studies addressed the potential effects of a multifactorial stress combination on plants, soils, and different microbial populations. Rillig *et al.* [30] examined the impact of multifactorial stress combination on soil properties and microbial populations. The effects of ten different stress factors associated with global warming, climate change, and environmental pollution were studied on soils, using different combinations of drought, low nitrogen, temperature, microplastics, glyphosate, antibiotics, fungicides, copper, salinity, and insecticides. It was found that an increase in the number of factors constituting a multifactorial stress combination (selected sets of one, two, five, eight, and ten stress factors) was accompanied by a decrease in the diversity of the soil microbiome, soil respiration, and other soil properties such as water-stable soil aggregates and decomposition rate (Figure 2A). Although previous studies proposed that such an effect would occur, Rillig *et al.* [30] were the first to demonstrate the negative effects of multifactorial stress combination on soil properties and microbial communities.

Examining the impact of a multifactorial stress combination on plants, Zandalinas *et al.* [31] subjected arabidopsis (*Arabidopsis thaliana*) seedlings to a combination of six different stresses, including heat, salt, high light, cadmium, acidity, and the herbicide paraquat (Figure 2B,C). In addition to studying the impact of multifactorial stress combination on plant growth and survival, this study also conducted a transcriptomic analysis of a selected set of multifactorial stress combinations and examined the impact of multifactorial stresses on the survival of different mutants impaired in reactive oxygen species (ROS) metabolism, as well as other metabolic processes and hormonal signaling pathways. Perhaps the most important finding of this study was that, although each of the different stresses, applied individually to plants, had a negligible effect on their growth and survival, the accumulated impact of multifactorial stress combination on plants was detrimental (Figure 2B,C). This finding is important because it demonstrates that different

Box 1. The Definition of a Multifactorial Stress Combination

We define a multifactorial stress combination as a combination of three or more ($n \geq 3$) stress factors simultaneously impacting plants. This definition takes the concept of a simple combination of two or at most three different stresses (e.g., drought and heat, salt and heat, drought, salinity and heat, or drought, heat and virus infection; e.g., [42,44,48,50]) and extends it to a combination of multiple factors. As depicted in the model presented in Figure I, the multiple stress factors that could simultaneously impact plants can be of biotic (e.g., virus, bacteria, insect), abiotic climate-driven (e.g., flooding, drought, heat), abiotic man-made anthropogenic (e.g., pesticides, antibiotics, heavy metals), or biotic/abiotic soil-associated (e.g., nutrient deficiency, salinity, decreased microbial diversity) origin. Any combination of three or more such factors, impacting plants simultaneously, is therefore defined as a multifactorial stress combination.

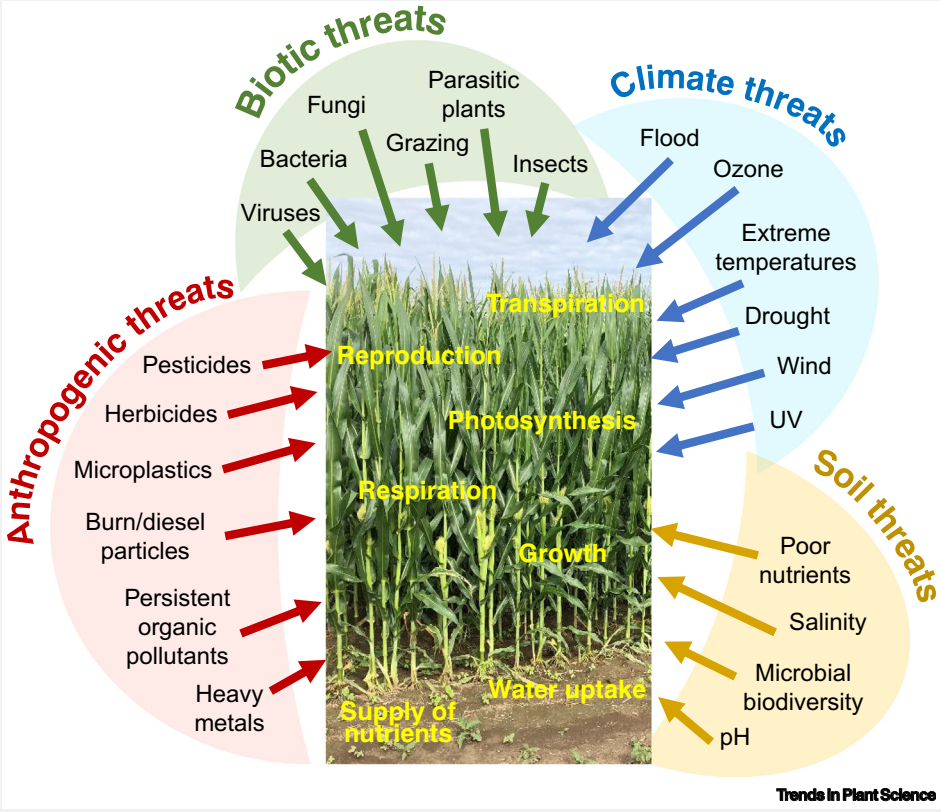

Figure I. The Definition of a Multifactorial Stress Combination.

stresses can interact to negatively impact plant health and performance, even if the effect of each stress applied individually is negligible. Multifactorial stress combination could therefore impact agricultural areas or ecosystems in ways that we may not be able to predict. For example, we may not be able to observe a clear decline in crop yields or ecosystems because of a low level of a single stress factor; however, once additional factors are introduced, even at low levels, they could negatively interact with each other and lead to dramatic decreases in agricultural productivity, as well as push ecosystems towards a rapid decline.

Together with the pioneering study of Rillig *et al.* [30], the results reported by Zandalinas *et al.* [31] therefore suggest that, with the increasing number of simultaneously occurring environmental stress factors in our environment, plant life, microbiomes, and soils are likely to deteriorate further (Figure 2). The similar trends observed in these two studies should serve as a dire warning to our society. Further altering our climate and polluting our environment could result in even higher

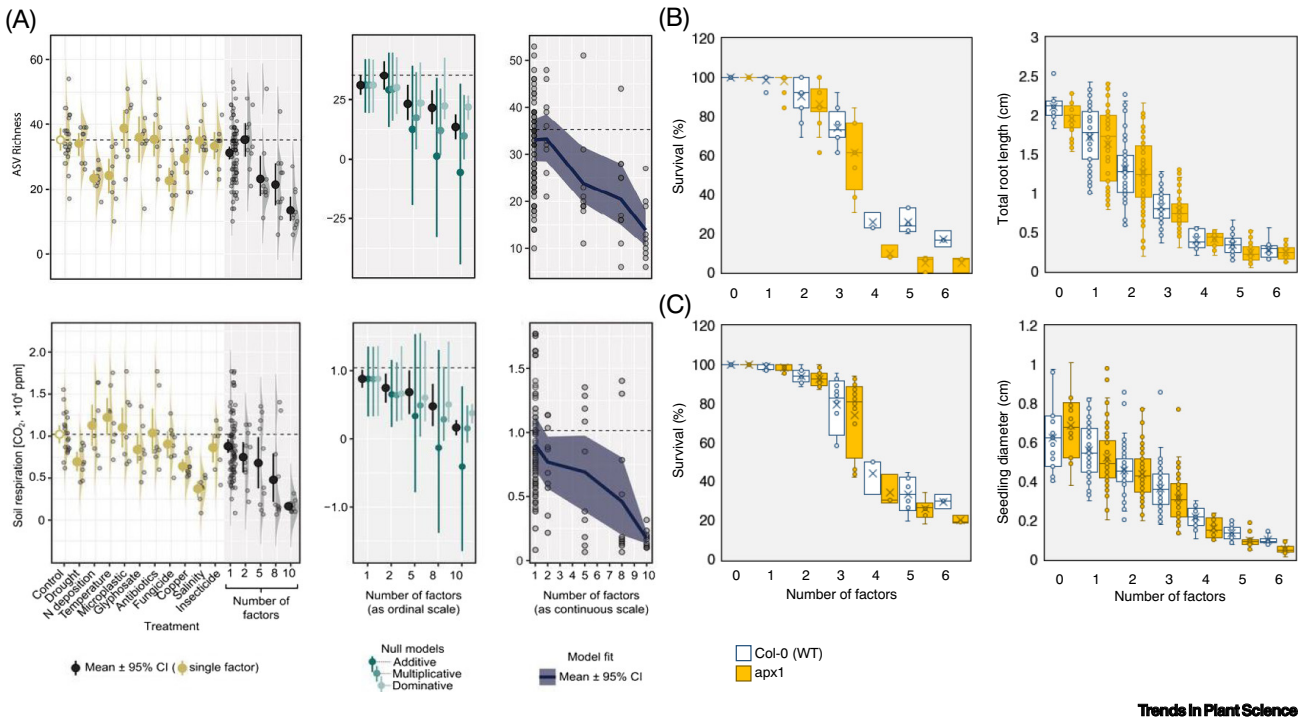

Figure 2. The Impact of Multifactorial Stress Combination on Plants, Soil, and Microbial Populations. (A) The impact of multifactorial stress combination on soil properties and microbial populations. (B) The impact of a combination of six different stresses on the survival and root growth of arabidopsis (*Arabidopsis thaliana*) seedlings (wild-type, Col-0, and mutants deficient in the hydrogen peroxide-scavenging enzyme ascorbate peroxidase 1, *apx1*) grown on agar plates. (C) The impact of a combination of six different abiotic stresses on the survival and growth of arabidopsis seedlings (similar to B) grown in peat soil. Graphs reproduced, with permission, from Rillig *et al.* [30] and Zandalinas *et al.* [31]. Abbreviations: APX1, ascorbate peroxidase 1; ASV, amplicon sequence variant; ppm, parts per million; WT, wild type.

complexities of multifactorial stress combinations that in turn would drive a crucial decline in plant growth, soil conditions, and overall agricultural productivity [30,31].

While the study of Rillig *et al.* [30] demonstrated that multifactorial stress combinations degrade soils (Figure 2A), Zandalinas *et al.* [31] demonstrated that the impact of multifactorial stress combination on plants is similar between plants growing in peat soil (Figure 2C) or on agar plates (Figure 2B). Plants growing in peat soil had an overall higher survival rate in response to all stresses and their combinations (providing a possible hint to the important role that the root microbiome could be playing in these processes), nevertheless the multifactorial stress combination impacted plants growing in peat soil in a similar manner to that for plants growing on plates (Figure 2B,C) [31]. These findings suggest that multifactorial stress combinations are likely to have a complex impact on different environments acting on soil microbiomes, plants, and their interactions.

The Impact of Multifactorial Stress Combinations on Plant Metabolism and Signaling

Previous studies of biotic and/or abiotic stress combinations involving two or at the most three different stressors [32–53] revealed that the response of plants to a state of stress combination is unique and does not simply represent the sum of the plant responses to each of the two or three different stresses that compose it. Although in some instances of combined stresses the response to one of the stressors included in the stress combination was more dominant than that to the other(s) (e.g., [42,43]), or the different stresses had an overall additive effect [41,50,54,55], in almost all studies conducted to date the response of plants to a stress combination included

transcripts, proteins, and metabolites that are unique to the combination (e.g., [42,44,47–52]). These findings were obtained through multiple omics [44,47–52] and genome-wide association studies (GWAS) [38–40] conducted in arabidopsis, as well as in other plants such as rice, corn, tomato, and soybean. Because different stresses may trigger different sensors, signal transduction pathways, hormones, regulatory networks, and/or metabolic responses that will lead to different acclimation and/or defense strategies (e.g., escape, avoidance, tolerance, senescence, and/or programmed cell death) (e.g., [35,41,42,56]), a combination of two or more stresses can have conflicting outcomes that could be reflected in the clashing of different strategies, networks, and/or pathways. In addition, the relative levels and functions of different stress hormones, such as ethylene, abscisic acid (ABA), jasmonic acid (JA), and salicylic acid (SA), in the response of plants to a particular stress could be conflicting when different stresses are combined (e.g., [45,52,57]). An example of this is revealed when comparing the stomatal responses of plants to the combination of drought and heat stress. During heat stress stomata open to cool leaves via transpiration, but during drought stomata close to prevent water loss. During a combination of drought and heat stress stomata of different plants remain closed, however, demonstrating that drought-driven regulation of stomata overcomes heat stress-driven regulation during a stress combination [44,45,52]. Interestingly, in a recent study on the combination of high light and heat stress it was found that heat stress-driven regulation of stomata (stomata opening) overcomes high light-driven stomata regulation (stomata closure) to result in stomata opening during the stress combination [47]. In addition to stomatal responses, root architecture is also altered during a stress combination [58,59], and nutrient availability plays a key role in this response [58,60,61]. In addition to studies examining the simultaneous exposure of plants to two or more stresses (described in the preceding text), studies of sequential exposure of plants to different stresses, or their combination, revealed a similar complexity in plant responses to a stress combination [61–63]. The developmental stage of the plant, circadian clock, plant nutrition, light quality, order of occurrence, and time of day could therefore play a key role in shaping the overall response of plants to a stress combination.

How the different pathways, networks, and hormones that regulate each of the plant responses to stress interact with each other, and how these interactions are regulated during a stress combination, are mostly open questions that await further research. There are many examples of signal transduction and hormone interactions in plants, including the integration of light and heat, or light and pathogen, signaling via different light receptors (e.g., [64]), the antagonistic functions of different plant hormones such as JA and SA (e.g., [45]), or the impact of epigenetic control over the activation of particular stress-response pathways (e.g., [65,66]). The identification of unique transcriptional regulators (transcription factors, TFs) and quantitative trait loci (QTLs) associated with stress combinations should begin to uncover some answers (e.g., [38–40,44,47–52]). A transcriptomic analysis of multifactorial stress combination of six different stresses revealed, for example, that even at this level of stress combination, different states of multifactorial stress combination induced unique sets of transcripts (Figure 3A) [31]. Moreover, it was found that, with the increased complexity of multifactorial stress combination (e.g., up to four different stresses), the number of transcripts responding to each individual stress decreased whereas the number of transcripts unique to each of the different stress combinations increased (Figure 3B) [31]. Interestingly, several common stress-response pathways, for example those involving heat-shock transcription factors (HSFs), the unfolded protein response (UPR), autophagy, and osmoregulation, activated by single stresses and some of their simple (two-factor) combinations, were not activated by particular (three to four-factor) stress combinations (Figure 3C,D) [31]. It is therefore possible that the function of these pathways is replaced by unique response pathways that are specific to these stress combinations, and/or that they are primarily regulated at the post-transcriptional level during multifactorial stress (Figure 3B) [31]. As indicated in the preceding text, further studies will be necessary to address

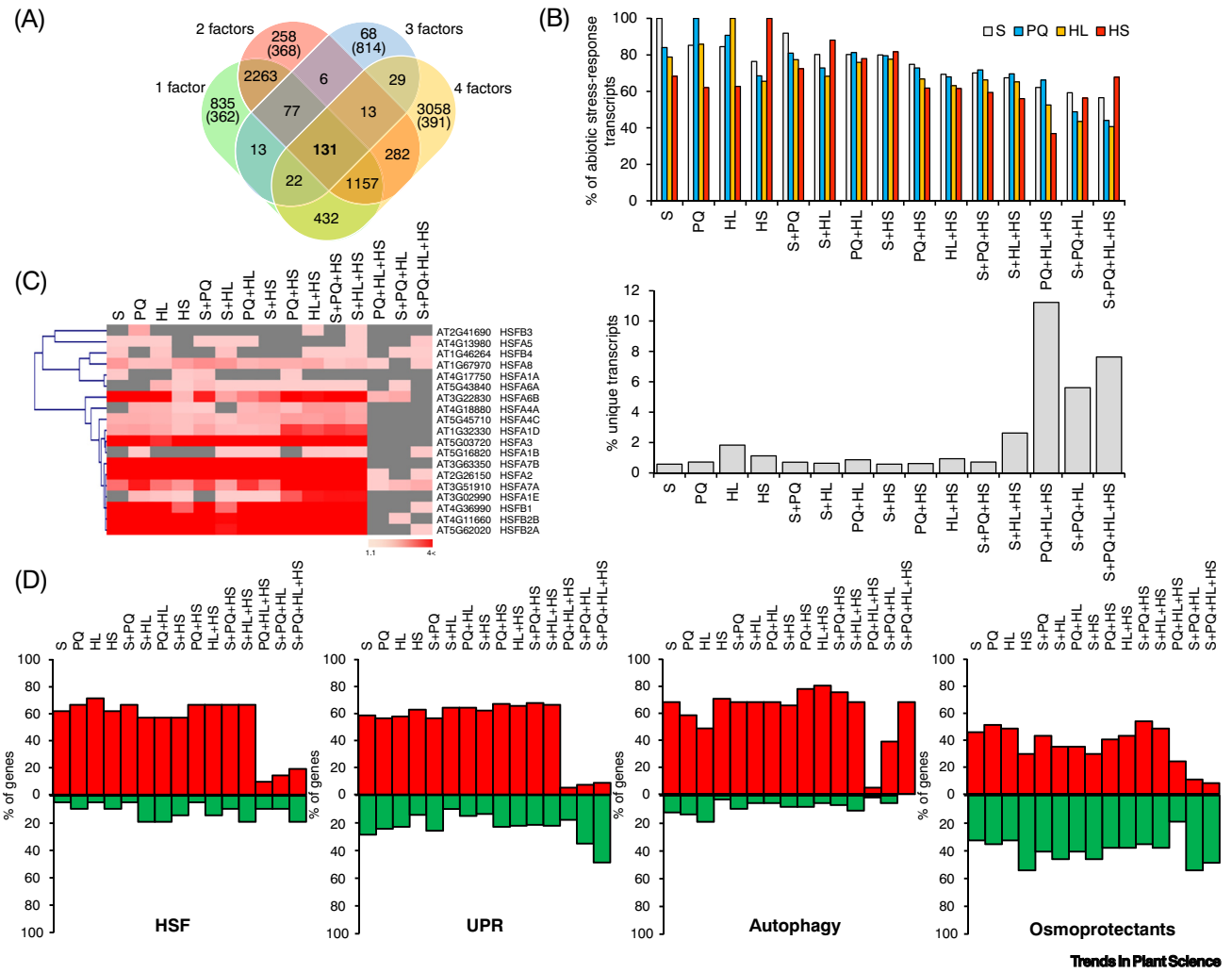

Figure 3. Transcriptomic Analysis of *Arabidopsis thaliana* Seedlings Subjected to Multifactorial Stress Combination of Four Different Stresses. (A) Venn diagram depicting the overlap between transcripts common or unique (in parentheses) to all one, two, three, and four different stress factors and their combinations, defining a multifactorial stress combination of four different stresses (salt, S; heat stress, HS; high light, HL; and the herbicide paraquat, PQ). (B) (Upper panel) Representation of S-, HS-, HL-, and PQ- induced transcripts in plants subjected to a multifactorial stress combination of S, HS, HL and PQ in all possible combinations. (Lower panel) Representation of unique transcripts (as % of the total number of transcripts significantly altered in response to each treatment) in plants subjected to a multifactorial stress combination of S, HS, HL, and PQ in all possible combinations. (C) Heat map showing the expression of all different heat-shock factors (HSFs) whose expression is altered in response to a multifactorial stress combination of S, HS, HL, and PQ in all possible combinations. (D) Representation of transcripts (up- or downregulated) involved in osmoregulation, autophagy, and HSF and unfolded protein response (UPR) pathways in the response of *Arabidopsis* seedlings subjected to multifactorial stress combination of S, HS, HL, and PQ in all possible combinations. Graphs reproduced, with permission, from Zandalinas *et al.* [31].

the complexity of acclimation/defense response integration during multifactorial stress combination (Figure 4A). However, from the limited studies conducted so far on multifactorial stress responses of microbial populations and plants, it is likely that new and exciting discoveries, relevant to ensure food, feed, and fiber production in a changing climate, could be made.

What Can We Learn from Extremophiles and Cancer Cells about Multifactorial Stress Combinations?

A state of multifactorial stress combination in plants might resemble the type of stress experienced by prokaryotic and eukaryotic cells living under extreme environments (i.e., extremophiles

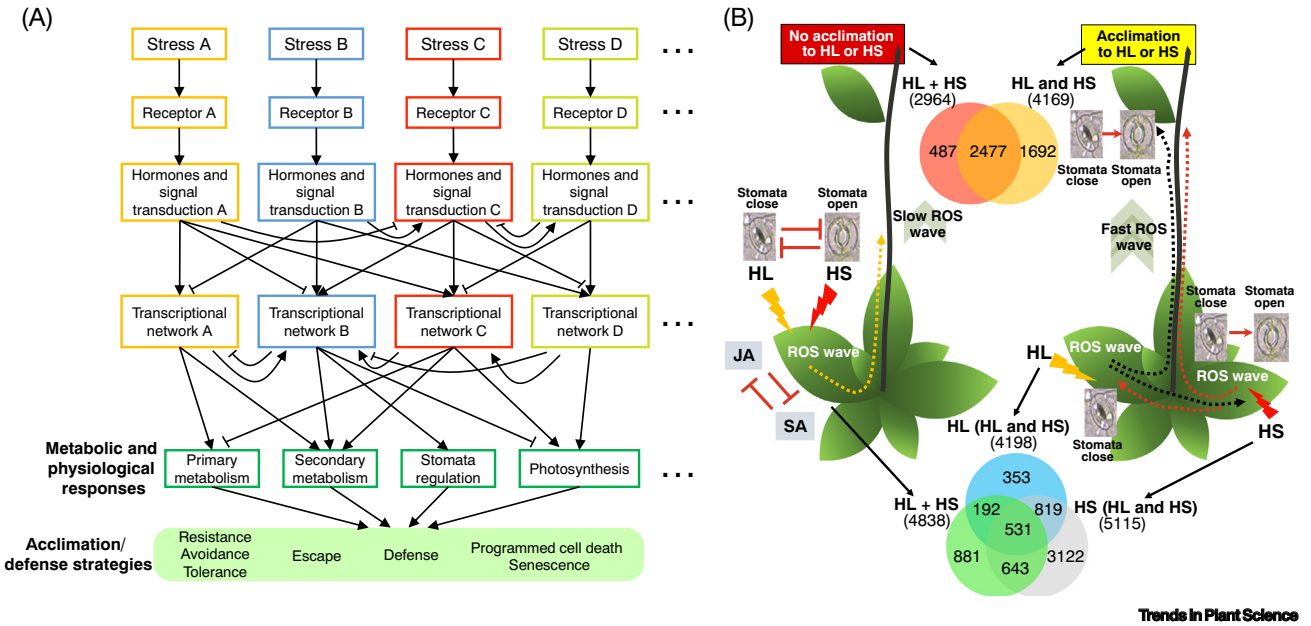

Figure 4. Integration of Different Stress Response and Systemic Signaling Pathways during Simple and Multifactorial Stress Combinations. (A) A hypothetical model depicting potential interactions between different signal transduction and acclimation/defense pathways coactivated in response to multifactorial stress combination in plants. (B) Integration of two different systemic signals in response to a stress combination. Two different scenarios are compared: two different stresses (high light, HL; and heat stress, HS) simultaneously applied to the same leaf (HL + HS; left), or to two different leaves (HL and HS; right). The two scenarios are different in the transcriptomic signatures, systemic reactive oxygen species (ROS) wave responses, and stomata and hormonal (jasmonic acid, JA, and salicylic acid, SA) responses they induce in local and systemic leaves. The model highlights the findings of Zandalinas *et al.* [45] that the way in which plants sense the different stresses that trigger systemic signals in response to a stress combination (i.e., at the same or different leaves) makes a significant difference to how fast and efficient they respond and acclimate.

such as some fungi, archaea, or bacteria that withstand a multitude of extreme environmental conditions) [67–70]. Exploring some of the mechanisms used by these organisms to withstand these conditions highlights processes such as DNA repair, protein repair and recycling, and maintaining free iron sequestered to prevent formation of ROS such as hydroxyl radicals [67–71]. A key role for balancing iron and ROS levels, cellular recycling via autophagy, and suppression of programmed cell death also emerges from studies of cancer cells that are rapidly evolving eukaryotic cells subjected to a multifactorial stress combination within the tumor microenvironment (i.e., a combination of acidity, anaerobic, nutrient, mechanical, immune response, and drug cytotoxicity stresses) (e.g., [72–79]). It is possible that acclimation to multifactorial stress conditions in plants might require similar mechanisms, and that these could be regulated by different multifactorial stress-specific transcriptomic networks. The observation that overexpressing the AtNEET protein in arabidopsis seedlings could mitigate some of the impacts of a multifactorial stress combination on plant growth lends further support to this possibility [31]. NEET proteins play a canonical role in maintaining iron and ROS homeostasis in plant and animal cells, and were found to overaccumulate in human epithelial breast cancer cells [73]. Furthermore, artificially elevating the expression levels of NEET proteins in cancer cells results in enhanced cancer cell resistance to oxidative stress and facilitates tumor growth [72]. Interesting parallels might therefore be drawn between plant, microorganism, and cancer cell survival under conditions of multifactorial stress conditions (e.g., the need to balance iron and ROS homeostasis). Moreover, it might be possible to harness some of the mechanisms used by cancer cells to survive within the tumor microenvironment [72–79], or by extremophiles to survive their natural environment [67–70], to enhance the tolerance of plants to multifactorial stress combination. In addition to extremophiles, plants, and cancer cells, the involvement of ROS in responses to stress combination was demonstrated in

the animal model *Caenorhabditis elegans* [80,81], further highlighting the importance of ROS signaling for cellular responses to stress combination.

Multifactorial Stress Combinations and Systemic Signaling

Systemic signaling describes the ability of plants to transmit a signal from a small group of cells located at a particular plant organ or tissue to the entire plant [82]. This process can be triggered by a local biotic or abiotic stress, and result in the activation of a defense or acclimation response in the entire plant (even in tissues that did not experience the initial stress stimulus). In a recent study of systemic signal integration during a stress combination, the impact of two local stress stimuli applied to the same, or two different leaves, of the same plant was studied in arabidopsis (Figure 4B) [45]. The two different stresses used (high light and heat stress) were found to induce a systemic response to the stress combination, but this response was much stronger and more successful in inducing systemic acclimation to high light or heat stress when the two different stresses were applied to two different leaves (Figure 4B) [45]. The transcriptomic and stomatal responses recorded in each of the different leaves and in the systemic tissues correlated with triggering a ROS wave that was much stronger when the two different stresses were simultaneously applied to two different leaves, as well as with the expected local and systemic responses to the individual (in each leaf) or combined (in the systemic leaf) stress combination [45]. This study revealed for the first time that different stresses impacting different parts of the plant can result in the integration of systemic signals that propagate to the systemic tissue and induce a systemic response to the stress combination. Interestingly, the plant hormones JA and SA played an antagonistic role in suppressing plant responses to the stress combination when the two stresses were applied to the same leaf (Figure 4B) [45]. Because plants, and especially large plants such as trees, are likely to experience multiple stresses at different organs and/or tissues simultaneously (Figure 4B) [45,82], these stresses might induce a state of readiness for multifactorial stress combination in the systemic tissue. Because systemic signal integration in response to a stress combination provides an ideal platform in which different local tissues, subjected to different stresses, as well as a single systemic tissue that responds to them, can be collected from the same plant, this experimental system could be used to enhance our knowledge of multifactorial stress combination and its potential to impact different pathways and hormones.

How Can We Develop Plants with Enhanced Tolerance to Multifactorial Stress Combinations?

Due to the conflicting nature of some of the acclimation and defense pathways and strategies that might be triggered during stress combination (Figures 3B–D and 4A) (e.g., [35,44,45,83]), achieving tolerance to a state of multifactorial stress might require focusing on common pathways and genes that function during all possible combinations of single and multiple stresses that compose the multifactorial stress condition (Figure 3A for four different abiotic stresses) (e.g., [31–37,44,47–53]). For example, some TFs and regulatory genes were found to respond to all six different stresses and their combinations in plants [31]. Another approach could be to augment the pathways and genes that are required for tolerance to extreme stress conditions or multifactorial stress combinations [31,67–79]. These might include, for example, pathways involved in sequestering iron and/or managing the relative levels of iron and ROS in cells, pathways involved in repair and recycling of proteins and DNA, or pathways that suppress metabolism and accumulate specific osmoprotectants [31,67–79]. One example of this approach is the overexpression of AtNEET in arabidopsis [31]. A completely different approach could be to focus on pathways and genes that are unique to a multifactorial stress combination [31]. An additional strategy could be to identify and study plants that are subjected to extreme and multifactorial stress conditions in nature (e.g., desert plants, plants growing under harsh conditions in industrial waste sites, salt marshes, and/or next to hot springs, and/or some invasive species) [84–86], and

attempt to import the pathways and genes used by these plants into some of our major crops. Altogether, a multitude of approaches and acclimation/adaptation strategies might be used, preferably exhibiting a high degree of plasticity. Finally, a promising approach to enhancing plant tolerance to multifactorial stress combinations could be the development of rhizosphere microbiome [87–91] inocula that will (i) tolerate multifactorial stresses themselves, and (ii) induce plant tolerance to multifactorial stress combinations. A possible source for such microbial communities could come from some of the same harsh environments used to identify plant strategies to combat multifactorial stress combinations, as discussed in the preceding text.

Prospects for the Future

Plants evolved for hundreds of millions of years in the absence of human interference. However, over the past 100–150 years humans have drastically impacted plants and rapidly altered their environment by introducing numerous new and sometimes extreme stressors and contaminants. In parallel to these processes, humans have been selecting and breeding plants for thousands of years to enhance their yield and other traits that make plants more suitable and supportive for humanity and our growing population. As described in the preceding text (Figures 1 and 2 and Box 1), these conflicting forces, or thrusts, set in motion by humans, are finally clashing, necessitating a serious effort on our side to prevent possible future disasters (see Outstanding Questions). The similar trends observed in the studies by Rillig *et al.* [30] and Zandalinas *et al.* [31], and the dramatic impact of multifactorial stress combinations on plants, soils, and microbial communities revealed by these studies (Figure 2) should serve as a dire warning to our society. Further polluting our environment could result in even higher complexities of multifactorial stress combinations that in turn could drive a crucial decline in plant growth, soil conditions, and overall agricultural productivity.

Outstanding Questions

At what point will we start feeling the effects of multifactorial stress combinations on different ecosystems and agricultural lands? Are they here already?

How do low levels of different abiotic stresses interact to negatively impact plant growth, survival, and yield?

How and to what extent does the timing, duration, intensity, and frequency of multifactorial stress combinations impact on the growth, productivity, and survival of plants?

How do different stress-specific sensors, signal transduction pathways, regulatory networks, and acclimation/defense strategies, that are coactivated during multifactorial stress combination, interact?

What are the key cellular processes and pathways that have a potential to improve plant survival and productivity (yield) in response to a multifactorial stress combination?

What important lessons can we learn from extremophiles and cancer cells about how to improve the tolerance of plants and crops to multifactorial stress combination?

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Declaration of Interests

The authors declare no conflicts of interest.

Supplemental Information

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