clearly distinguished from the other samples analyzed, and displayed a 1.5–2-fold greater increase in cell number, mainly at the later time points of the curve (Figure 1b, Supplementary Figure 1b), and reduced response to the antiproliferative effect of rapamycin, a specific mTOR inhibitor (Figure 1c, Supplementary Figure 1c). Curiously, whereas dual PI3K-mTOR inhibition (wortmannin-rapamycin treatment) continued to be less effective in reducing to a similar extent the proliferation of ASD1–2 and control cells, it was able to restore the enhanced proliferation of ASD3 cells (Figure 1c, Supplementary Figure 1c), suggesting a possible different regulatory mechanism in ASD3 cells. Knockout mouse models of both syndromic and nonsyndromic ASD with disinhibited mTOR signaling and dysregulated protein synthesis present dysplastic and enlarged neurons with increased spine density in several brain regions. Although we did not notice increased ASD1–3 SHED volumes, it will now be important to determine and explore further whether the altered proliferative phenotype observed in these cells may also be observed in neuronal cell types, which could be a potential additional mechanism whereby disrupted mTORC1 signaling contributes to ASD neuropathology.

Conventional karyotyping and analysis of copy number variations at 15q11-q13, 16p11 and 22q13, found to occur more often in ASD, did not reveal any genomic aberrations in all patients except ASD3, who presents an inverted duplication of 15q11-q13. It is possible that genes located at this region may contribute to the aberrant molecular and cellular phenotypes observed in ASD3 cells. In addition, TSC1/2, FMR1, PTEN, NF1 and MeCP2 genes (ASD-associated genes known to be negative regulators of PI3K-mTOR signaling pathway) were screened for potentially deleterious variants. We identified MeCP2 variants in patients except ASD3, who presents an inverted duplication of 15q11-q13. These findings indicated that smaller anterior cingulate cortex volume was a preexisting vulnerability factor for posttraumatic stress disorder (PTSD) symptoms and that decreased volume of the orbitofrontal cortex (OFC) was a result of posttraumatic growth and self-esteem. Furthermore, we also assessed the subjects’ psychological characteristics, including anxiety, depression, posttraumatic growth and self-esteem. Furthermore, we

RESILIENCE AFTER 3/11: STRUCTURAL BRAIN CHANGES 1 YEAR AFTER THE JAPANESE EARTHQUAKE

Stressful events can have both short- and long-term effects on the brain. A recent investigation by our lab identified regional grey matter volume (rGMV) changes in people in the months following the Japanese earthquake. These findings indicated that smaller anterior cingulate cortex volume was a preexisting vulnerability factor for posttraumatic stress disorder (PTSD) symptoms and that decreased volume of the orbitofrontal cortex (OFC) was a result of these acquired symptoms. These types of symptoms were regarded as manifestations of the short-term effects of post-earthquake stress. However, the long-lasting effects of stressful events on brain structures remain unclear. Thus, this study examined the 1-year prognoses of subjects after a stressful event to clarify the long-term effects of stress on structural brain changes.

Of the 42 subjects included in our previous study, 37 subjects (male/female (M/F) = 28/9, age = 21.0 ± 1.6 years) were recruited for a third time, and their structural magnetic resonance imaging (MRI) scans were evaluated 1 year after the earthquake. The optimized voxel-based morphometry (VBM) method for a brain structural data set (for greater detail, see Sekiguchi et al.,) was applied, and rGMVs from before (Pre), soon after (Post) and at the 1-year follow-up (Follow-up) of the earthquake were compared using conjunction analyses. In addition, we also assessed the subjects’ psychological characteristics, including anxiety, depression, posttraumatic growth and self-esteem. Furthermore, we

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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In contrast, stress related to the earthquake may persist even after 1 year. Psychological evaluations at 1 year revealed that even subclinical levels of depression and anxiety levels had not improved from soon after the earthquake. Hippocampal volume reduction is a robust finding in traumatized subjects, and is observed even in subjects with subclinical depression after a disaster. Even if the hippocampal volume of young healthy adults were not significantly but slightly reduced as a function of aging (see Supplementary Discussion), post-earthquake stress would accelerate the hippocampal volume reduction because age-related reduction is modified by PTSD and depression. Together, these findings led us to hypothesize that both prolonged stress and aging affect a reduction in hippocampal volume over time, whereas short-term stress does not reduce hippocampal volume in the period immediately following stressful events such as earthquakes (see Supplementary Discussion).

The limitations of this study included the absence of psychological assessments and incomplete profiles for the control subjects (see Supplementary Discussion).

Despite these limitations, the present follow-up VBM study found that stressful events had long-lasting effects on various brain structures, suggesting that such changes are influenced by prolonged stress and self-esteem characteristics. Here, it was assumed that structural changes in the brain following stressful life events are not static, but dynamic, throughout one’s lifetime. Recently, altered functional and structural connectivity, including in regions adjacent to the OFC and hippocampus as well as in the insula, basal ganglia and parietal lobes, have been reported soon after a disaster. Therefore, further longitudinal investigations using multimodal approaches are necessary to examine whether the stress-induced alterations in brain structure are reversible (see Supplementary Discussion).

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
All authors contributed to the concept and design of the study. AS, YK, MS, TA, SH, SN, and CMM contributed to data acquisition. AS, YK, RN, HT, TA, YT and RK contributed to the data analysis and interpretation. AS, MS, RN, HT, TA, YT and RK provided statistical expertise. AS wrote the manuscript. MS, RN, HT, YT and RK reviewed/revised the manuscript. All authors discussed the results and commented on the manuscript. All authors gave their final approval for the manuscript to be submitted.

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