associated with schizophrenia; in controls, eight (2%) were supposed to be associated with schizophrenia (Table 2). Moreover, among the five SchizophreniaGenes impacted in cases, three were in deleted state and two were in duplicated status; whereas among the eight SchizophreniaGenes affected in control, only one gene was deleted state and other seven were all in duplicated status (Table 2).

We carried out a genome-wide scan for structural variants greater than 100 kb on genomic DNA of 342 individuals. Our sample set included 155 schizophrenia patients and 187 normal controls. In Walsh *et al.*'s study, 150 cases and 268 controls were recruited for the main analysis. Thus, the sample size is close to each other, especially the case samples.

Unlike Walsh *et al.*'s study, we found no trend of significant difference of all CNVs ($P=1.00$) or all rare CNVs (frequency $<1\%$, $P=0.70$) or rare CNVs affecting genes ($P=0.46$) between cases and controls. In our 155 cases, 22 carried rare CNVs deleting or duplicating or disrupting genes, whereas 38 of 150 patients carried gene-related rare CNVs in Walsh *et al.*'s study; in our 36 patients with onset age not more than 18, only 5 carried gene-related rare CNVs, whereas 25 of 76 such patients had gene-related rare CNVs in Walsh *et al.*'s study. Obviously, our cases tended to have less gene-related CNVs than the previous study.

Referring to the SchizophreniaGene Database, we studied the distribution of rare CNVs affecting schizophrenia susceptibility genes. We found that 5 of 96 genes impacted by rare CNVs were SchizophreniaGenes in cases (5.2%), whereas 8 of 399 genes affected by rare CNVs were SchizophreniaGenes in controls (2.0%). Moreover, three of those five genes in cases were in deleted status, and only one of eight genes in controls was in deleted status. Given that the deleted status could have more effect on gene function, much larger sample size should be used to replicate this trend of difference.

However, our results do not support Walsh *et al.*'s main finding that rare CNVs deleting, duplicating or disrupting genes happens more frequently in schizophrenia patients, especially schizophrenia patients with small onset ages (onset age $\leqslant 18$ in their study). Though different population might have genetic heterogeneity of disease etiologies, we need to be more prudently to decide whether rare CNVs play a big role in schizophrenia etiology. Much larger number of samples were suggested to study such low frequency variants in the future.

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Social isolation potentiates cell death and inflammatory responses after global ischemia

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Social integration is fundamental for good emotional and physical health. Indeed, socially isolated individuals with low perceived social support are at increased risk for many health conditions (reviewed in references Hawkley and Cacioppo[1] and House *et al.*[2]), including cardiovascular disease.[3–5] Development of animal models is required to understand the specific physiological mechanisms responsible for the effects of social isolation on health. Here, we provide evidence that social isolation in mice potentiates the pathophysiological responses to cardiac arrest (CA), which may explain, in part, why social isolation is as strong a predictor of 1-year mortality among acute myocardial infarction patients as some of the classic physiological risk factors, including high blood cholesterol concentrations and hypertension.[5]

To determine the impact of social environment on neuroinflammation, neuronal death and corticosteroid concentrations after global ischemia, we housed adult male C3H/e mice either alone (isolated, $n=7$) or five per cage (social, $n=5$) beginning 2 weeks prior to

inducing 8 min of CA, followed by resuscitation by epinephrine injection and chest compressions (CA/ CPR (cardiopulmonary resuscitation)); complete description in Neigh *et al.*[6]). The control group consisted of mice that underwent the same cardiac arrest procedure, but ischemic influences on the brain were prevented through the use of hypothermia;[6] hypothermic-isolated ($n=10$) and hypothermic-social ($n=7$) groups were collapsed into a single control group because they were not significantly different on any measure ($P>0.05$ in all cases). Brain tissue and blood samples were collected either 24 h or 7 days after CA/CPR for gene expression or histological analysis, respectively. As expected, cardiac arrest induced neuronal degeneration throughout the hippocampus; however, the extent of damage was significantly increased among mice that were socially isolated prior to CA/CPR (Figure 1a, b and e). Specifically, CA/CPR evoked more neuronal degeneration (that is, Fluoro Jade-positive neurons (FJ+)) in the CA1 field ($F_{2,24}=20.15$, $P<0.0001$; Figure 1e), CA2 field ($F_{2,24}=21.14$, $P<0.0001$) and dentate gyrus ($F_{2,24}=16.06$, $P<0.0001$) of socially isolated versus socially housed and control mice. Social isolation also exacerbated the post-ischemic inflammatory responses throughout the hippocampus (Figure 1c, d, f and g). Microglial activation (that is, MAC-1 staining) following CA/CPR was higher in the CA1 field ($F_{2,28}=26.68$, $P<0.0001$; Figure 1f), CA2 field ($F_{2,28}=12.29$, $P<0.0001$), dentate gyrus ($F_{2,28}=20.56$, $P<0.0001$) and subiculum ($F_{2,28}=31.06$, $P<0.0001$) of socially isolated mice than socially housed mice and control ($P<0.05$). Furthermore, mRNA expression of the proinflammatory cytokine tumor necrosis factor-α (TNF-α), measured 24 h after resuscitation, was significantly elevated in isolated mice, but not socially housed mice, relative to the control mice ($F_{2,18}=4.83$, $P<0.0001$; Figure 1f). Upregulation of

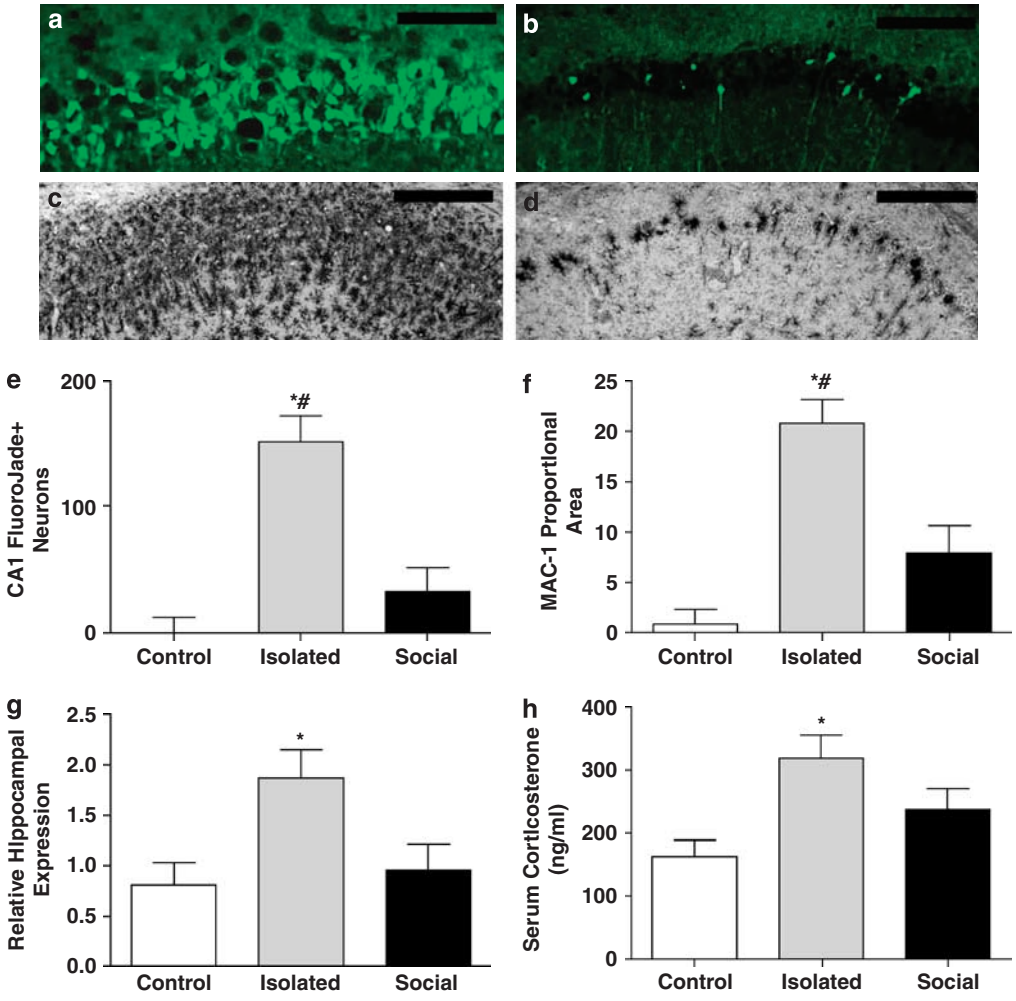

Figure 1 Social isolation potentiates ischemic damage. Fluoro Jade staining of hippocampal cell degeneration in socially isolated (**a**) and socially housed mice (**b**). Microglial activation in the socially isolated (**c**) and socially housed animals (**d**). Summary (mean ± s.e.m.) of histological outcomes in the ischemia-vulnerable CA1 region; Fluoro Jade staining (**e**) and proportional microglial staining (**f**). mRNA expression of the proinflammatory cytokine tumor necrosis factor-α (TNF-α; mean ± s.e.m.) 24 h after reperfusion (**g**). Circulating corticosterone (mean ± s.e.m.) 24 h after reperfusion (**h**). An asterisk (*) indicates significantly different means from the control groups ($P<0.05$), whereas a pound (#) indicates significantly different means from the social group ($P<0.05$).

microglia and the neurotoxic mediators they release, including TNF-α, in the developing ischemic lesion can contribute to secondary neuronal damage and infarct evolution.[7] Thus, the near-complete attenuation of the inflammatory responses to cerebral ischemia in socially housed mice likely contributed to the observed reduction in neuronal damage (Figure 1a, b and e).

Social context also influenced early post-ischemic corticosterone concentrations. Isolated mice had significantly elevated serum corticosterone concentrations 24 h after ischemia relative to the control mice ($F_{2,20} = 4.32$, $P < 0.0001$; Figure 1h). Elevated post-ischemic corticosteroid concentrations have previously been linked to increased neuronal damage,[8,9] and may have contributed to the elevated neuronal death among the isolated mice relative to the socially housed cohort.

Together, these data indicate that the pathophysiological responses of socially isolated and socially integrated mice to CA/CPR are quantitatively and qualitatively different; social isolation potentiates ischemia-induced neuronal damage, neuroinflammation and corticosteroid secretion, three important determinants of outcome following CA/CPR. The elevated inflammatory responses among socially isolated individuals also may indirectly compromise recovery by contributing to the development of post-ischemic affective disorders.[10] Given the well-described influence of social relationships on health, and this new evidence that social isolation alters the physiological response to cardiac arrest, we emphasize the need for additional research aimed at characterizing and promoting the types of social relationships that promote health in humans, and the value of monitoring physiological measures in these studies.

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Effect of disrupted-in-schizophrenia-1 on pre-frontal cortical function

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Several linkage and genetic association studies have implicated the disrupted-in-schizophrenia-1 (*DISC1*) gene as influencing susceptibility to schizophrenia, and bipolar disorder,[1] but relatively little is known about its effect on brain function. DISC1 is expressed in centrosomes, mitochondria, the cytoplasm of postsynaptic spines, and actin stress fibers of cerebral cortical neurons.[1] It interacts with proteins involved in cell division, cytoskeletal organization and intracellular transport, including PDE4B, which has been linked to learning and memory, and Ndel1, a key regulator of neuronal migration and a putative target of anti-psychotic drugs.[1] Knockdown of *DISC1* perturbs neurite outgrowth *in vitro*,[1,2] and cortical neuronal migration and dendritic arborization *in vivo*.[1] Over-expression of DISC1 leads to enhanced neurite growth *in vitro*,[1] whereas expression of mutant human DISC1 in mice is associated with behavioural abnormalities, ventricular enlargement and attenuation of cortical neurite outgrowth.[3]

Abnormal pre-frontal function is a robust pathophysiological feature of psychotic disorders, and may underlie many of the associated symptoms and cognitive deficits.[4] A risk gene for these disorders would therefore be expected to influence pre-frontal function. We used functional neuroimaging to test the hypothesis that DISC1 would significantly influence pre-frontal function in healthy volunteers. Functional magnetic resonance imaging was employed to measure regional brain activation during a verbal fluency task, a classical test of pre-frontal function which requires the generation of words from letter cues.[5] Execution of this task is normally associated with prominent pre-frontal activation, particularly in the left hemisphere.[5] In patients with psychotic disorders, task performance is impaired and pre-frontal activation is altered.[4] We scanned 53 healthy volunteers consisting of 27 Cys704 carriers (including 7 Cys704 homozygotes) and 26 Ser704 homozygotes (Supplementary Table S1; Supplementary Materials and Methods). Demographic features (intelligence quotient, years of education, gender, handedness and ethnicity) were not different between genotype groups (at $P < 0.05$) except for age ($F = 4.27$, $P = 0.044$) which was therefore used as a covariate of no interest. Subjects articulated responses out loud, permitting on-line recording of task performance. We selected the Ser704Cys polymorphism, encoded by the rs821616 single-nucleotide polymorphism (SNP), as this coding and