integer values between one and five rather than asking for explicit probabilities, as has been done previously. With this, they might have side-stepping issues of probability calibration and risk sensitivity. Second, they claim that asking for confidence reports after the choice rather than at the same time avoids divided attention between confidence reporting and choice. However, it has previously been shown that in the presence of a stream of evidence, as is the case in their click-rate discrimination task, evidence presented close to the choice might be processed further after choices have been made (Resulaj et al., 2009). This could cause confidence reports to be based on different evidence than that used to make the choices (Zylberberg et al., 2012). In this light, it remains to be seen if it was indeed the asynchronous choice and confidence report that caused these reports to match the statistical model. It might in fact explain why, for this particular task, confidence judgments appeared noisier than predicted by the noise-free model.

An interesting observation made by Sanders and colleagues is that the human confidence judgments in the click-rate discrimination task are a function of both the decision time (that is, the duration between stimulus onset and choice) and the difficulty of the trial, as measured by the difference in click rates across ears. This is compatible with previous empirical findings (Kiani et al., 2014), but at odds with simple ideal-observer models that predict that confidence should only depend on decision time, irrespective of trial difficulty (Drugowitsch et al., 2012; Kiani and Shadlen, 2009). These models are based on the same statistical framework as that of Sanders and colleagues, such that it needs to be clarified how these seemingly contradictory findings can be brought in line.

This should not distract, however, from their important main findings that human confidence reports indeed feature the same hallmarks as confidence computed according to the principles of statistical decision theory. Hence, these reports might arise from the same computations that underlie our decisions under uncertainty, thus suggesting confidence to be a central and integral component of everyday decisions, rather than just an afterthought.

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C9ORF72-ALS/FTD: Transgenic Mice Make a Come-BAC

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For five years, since the landmark discovery of the *C9ORF72* hexanucleotide repeat expansion in ALS/FTD, a transgenic mouse model has remained elusive. Now, two laboratories (Liu et al., 2016; Jiang et al., 2016) report the development of BAC transgenic mice that recapitulate features of the human disease.

Discovered in 2011, the GGGGCC hexanucleotide repeat expansion (HRE) in *C9ORF72* is now regarded as the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The HRE, located in the first intron, consists of 2–30 repeats in the general population and can range from hundreds to thousands of repeats in affected patients. Difficult to clone and prone to germline and somatic instability, these large expansions have presented a technical hurdle for the development of transgenic

mouse models. In fact, the field has been largely advanced through studies of autopsy tissue and patient-derived iPS neurons, providing some evidence for pathophysiology, e.g., nucleocytoplasmic transport, and including the first candidate antisense oligonucleotide and small-molecule therapies (for a recent review, see Todd and Petrucelli, 2016). As powerful as the "true" human models are, having intact rodent models provides a multiplicity of additional benefits. Early attempts using a bacterial artificial chromosome (BAC) to express part (Peters et al., 2015) or all (O'Rourke et al., 2015) of the human C9 gene produced mice with characteristic molecular abnormalities (RNA foci, repeat-associated non-ATG [RAN] dipeptides) but no clinical or neuropathologic phenotype. Alternative approaches, using viral delivery of short HREs (Chew et al., 2015) or dipeptide repeat proteins (DPRs; Zhang et al., 2016), generated very provocative results, but with synthetic constructs and high levels of RNA and DPR overexpression. Now, two groups, Jiang et al. (2016) and Liu et al. (2016), report the development of BAC transgenic mice that use patient-derived gene constructs to recapitulate molecular, neuropathologic, and clinical features of C9-ALS/FTD. These mice will be valuable for studying disease mechanisms and testing therapeutics. Moreover, careful comparison between these models may yield additional insights into C9 pathogenesis.

The C9 protein is a DENN domain-containing protein that may play a role in endosomal trafficking. The issue of whether the C9 HRE causes disease by a loss or gain of function (or both) remains an open question. Numerous groups have reported that C9 mRNA expression is reduced in patient tissue (DeJesus-Hernandez et al., 2011 and others), and C9 protein levels are also reduced in frontal cortex (Waite et al., 2014). Despite early reports of motor defects in invertebrate knockout models, conditional (Koppers et al., 2015) and germline (Atanasio et al., 2016; O'Rourke et al., 2016) ablation of the mouse homolog of C9 has been insufficient to cause neurodegeneration.

In this issue, Jiang et al. present findings from another germline knockout, which, as previously reported, develops dramatic hematopoietic abnormalities, with splenomegaly, lymphadenopathy, and premature death. Although 12-month-old null mice have mild deficits in social interaction and Rotarod performance, they do not show EMG abnormalities or spinal motor neuron loss. Brain pathology was not evaluated in the current study, but was absent in a similar model at 17 months (O'Rourke et al., 2016), suggesting these behavioral deficits may be more related to systemic illness than neurodegeneration. The heterozygous mice, more analogous to the human disease, show no pathological or behavioral phenotype. Interestingly, O'Rourke et al. did show an alteration in macrophage function and pathology, as reflected in a common aberrant transcriptome in the CNS of null mice and patient brain tissue, hinting that loss of C9 function could produce an altered neuro-inflammatory response. In aggregate, these rodent studies suggest that loss of function is unlikely to be a strong contributor to C9-ALS/FTD and that the gene may have a more profound role in hematopoietic function. However, no study to date evaluates the partial loss of C9 in the setting of the HRE.

Two C9 gain-of-function mechanisms, RNA toxicity and accumulation of RAN-translated DPRs, have received significant attention. Fluorescence in situ hybridization (FISH) reveals accumulation of sense (G_4C_2) and antisense (C_4G_2) RNA foci in patient tissue (DeJesus-Hernandez et al., 2011; Zu et al., 2013), and the C9 HRE sequesters RNA binding proteins, including regulators of nucleocytoplasmic trafficking and other fundamental processes (Donnelly et al., 2013). Antibodies to all six predicted products of C9 RAN translation (poly-GP, -GA, and -GR in the sense direction, and poly-GP, -PA, and -PR in the antisense direction) label inclusions in autopsy tissue (Zu et al., 2013). Genetic overexpression or exogenous delivery of DPRs causes toxicity in vitro and in vivo. However, the data conflict about which DPRs are most toxic. Since the precise mechanism of RAN translation in C9 is unknown, it has also been difficult thus far to experimentally separate the relative contributions of RNA gain of function versus RAN translation to C9-mediated neurodegeneration in model systems with human levels of expression.

Perhaps due to a high degree of variability, studies in autopsy tissue have failed to demonstrate a consistent effect of HRE length or C9 expression level on RNA foci or DPRs. The precise correlation between these molecular features and disease severity is also unclear, although patterns are starting to emerge in larger cohorts. Complicating matters are two recently generated BAC transgenic mice, both of which display RNA foci and DPRs, yet fail to develop a phenotype or neuropathology (O'Rourke et al., 2015; Peters et al., 2015). These studies raise the question of whether RNA foci and DPRs are insufficient to drive neurodegeneration (and may even be protective), or whether additional genetic or epigenetic factors are required to cause pathology.

To address these questions, Jiang et al. developed multiple BAC transgenic lines using a construct containing C9 exons 1–5 (with 140-kb 5′ flanking sequence). Four lines were characterized, expressing 110 and 450 repeats (with increasing expression levels, designated 450A–C). As in previous studies, these mice did not show evidence of motor neuron disease. No deficits in weight, grip strength, or Rotarod performance were seen out to 18 months of age, and there were no deficits in resting EMG or myogenic motor-evoked potentials at 12 months. No motor neuron loss or gliosis was seen in the spinal cord or motor cortex.

However, a cognitive phenotype was detected. Lines 450B–C developed spatial learning and working memory deficits as well as increased anxiety. In 450B–C, but not 110 or 450A, mild loss of neurons was also seen in the hippocampus. No gliosis or TDP-43 mislocalization was observed, although increased phosphorylated TDP-43 was seen by western blot. RanGAP1 and Lamin B staining, recently implicated in C9 human brain, iPS neurons, and fly models, did not reveal nuclear pore pathology. Both sense and antisense RNA foci were detected, and there was a strong effect of C9 expression on foci density. Aggregates of sense but not antisense DPRs were detected by immunohistochemistry. Quantitative analysis by ELISA showed a strong correlation between repeat number, C9 expression, and poly-GP levels.