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Acknowledgements

We thank M. Ahissar, and S. Barash for suggestions; A. Arieli, F. F. Ebner, K. O. Johnson, R. Malach and D. J. Simons for comments and discussions; M. E. Diamond for assistance during our initial thalamic recordings; and B. Schick for reviewing the manuscript. This work was supported by the US–Israel Binational Science Foundation and by the MINERVA Foundation, Germany. S.H. was supported by The Centre for Absorption of Scientists, Ministry of Absorption, Israel.

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Presenilin is required for proper morphology and function of neurons in *C. elegans*

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Mutations in the human presenilin genes cause the most frequent and aggressive forms of familial Alzheimer's disease (FAD)[1]. Here we show that in addition to its role in cell fate decisions in non-neuronal tissues[2–4], presenilin activity is required in terminally differentiated neurons *in vivo*. Mutations in the *Caenorhabditis elegans* presenilin genes *sel-12* and *hop-1* result in a defect in the temperature memory of the animals. This defect is caused by the loss of presenilin function in two cholinergic interneurons that display neurite morphology defects in presenilin mutants. The morphology and function of the affected neurons in *sel-12* mutant animals can be restored by expressing *sel-12* only in these cells. The wild-type human presenilin PS1, but not the FAD mutant PS1 A246E, can also rescue these morphological defects. As *lin-12* mutant animals display similar morphological and functional defects to presenilin mutants, we suggest that presenilins mediate their activity in postmitotic neurons by facilitating Notch signalling. These data indicate cell-autonomous and evolutionarily conserved control of neural morphology and function by presenilins.

To study the activity of presenilin genes in neurons, we focused on *C. elegans sel-12* as the detailed morphology and function of many neurons in *C. elegans* is known. Like presenilins in other species, *C. elegans* sel-12 is strongly expressed in neurons. We tested the functional integrity of the nervous system of *sel-12* mutants by looking for defects in the execution of a variety of behaviours, such as movement and response to mechanical, chemical and thermal stimuli.

We found that *sel-12* mutants display a highly penetrant defect in their ability to sense and/or memorize temperature. Wild-type *C. elegans* display strong preference for their growth temperature, and can memorize it and store the information for several hours, suggesting a neuronal plasticity[5]. This behaviour can be studied with a simple experimental model. When placed in a radial thermal gradient on the agar surface of a petri dish, wild-type animals migrate to their preferred temperature, and then move in isothermal circles (Table 1, Fig. 1a). In contrast, the *sel-12(ar131)* and *sel-12(ar131)* and *sel-12(ar171)* mutant animals have lost the ability to perform isothermal tracks. Most animals are non-responsive to the temperature gradient and moved randomly on the plate (athermotactic behaviour), and 10% of the remaining animals moved to colder temperatures than the wild-type (cryophilic behaviour). These results indicate that *sel-12* mutants may have defects in the neural circuit for thermotaxis.

The neurons necessary for thermotaxis have been studied extensively by mutational analyses and laser ablation studies[6]. Temperature input activates the two AFD sensory neurons, which synapse extensively onto the two AIY interneurons. Chemical signals from AIY and AIZ (synaptic partners that represent the four central integrating interneurons), in turn, regulate postsynaptic inter- and motor neurons that control the motor response. We carefully examined the morphology of the AFD, AIZ and AIY neurons in *sel-12* animals using green fluorescent protein (GFP) reporter constructs, and saw no obvious defects in AFD and AIZ neurons (data not shown). However, we identified defects in the morphology of AIY neurons (Table 2, Fig. 2). In wild-type animals, the processes of both AIY neurons extend anteriorly from the cell bodies along the ventral cord, run around the nerve ring and meet and terminate at the dorsal midline[7] (Fig. 2e). In adult *sel-12* mutants the AIY cell bodies are correctly positioned in the head ganglion. However, the AIY axons often grow too far anteriorly before turning and fasciculating in the nerve ring (Fig. 2d), and/or do not stop growth at the dorsal side of the nerve ring, but turn posteriorly, sometimes extending up to the midbody region (Fig. 2b–d, classified as severe defects in Table 2). In addition, short extra neurites often emerge directly from the cell soma or branch off the primary process (Fig. 2a, classified as minor defects in Table 2). The number of animals showing these types of defects in AIY morphology was higher in *sel-12(ar171)* mutants (35% defects) than in *sel-12(ar131)* mutants (20% defects; Table 2). This is consistent with the severity of these mutations and their effect on egg-laying behaviour (*ar171* carries a nonsense mutation in *sel-12* and genetically represents a null allele, and *ar131* carries a missense mutation in *sel-12*)[2]. Behavioural defects are far more penetrant than the morphological defects, indicating that *sel-12* animals may also have more subtle defects in the AIY neurons than can be visualized with GFP

Table 1 Rescue of the *sel-12* thermotaxis defect

Genotype	Transgene	Fraction showing isothermal tracks
Wild type*		41/46
sel-12(ar131)		1/42
sel-12(ar171)		3/38
hop-1(lg1501)		0/44
lin-12(n941)		0/15
hop-1(lg1501);sel-12(ar131)		0/31
hop-1(lg1501);sel-12(ar171)		0/33
sel-12(ar171);byIs101	*sel-12::sel-12*	38/49
sel-12(ar171);byIs100	*sel-12::sel-12*	19/41
Wild type†		49/55
sel-12(ar131)†		3/40
sel-12(ar171)†		2/39
sel-12(ar131); byEx103†	*ttx-3::sel-12*	18/42
sel-12(ar131); byEx115†	*ttx-3::sel-12*	21/41
sel-12(ar131); byEx115†	*ttx-3::sel-12*	35/67
sel-12(ar171); byEx115†	*ttx-3::sel-12*	18/41

* Strain carries a *daf-6(e1377)* mutation that did not affect thermotaxis behaviour.
† Animals expressing *ttx-3::GFP*.
byIs100 and *byIs101* are independent chromosomally integrated arrays expressing *sel-12* cDNA from the *sel-12* promoter.