

Summary of the Doctoral Thesis for the
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Regulation of cortical activity through inhibitory interneuron plasticity

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Summary of the scientific work

In this thesis, I will summarize recent developments in the field of “synaptic long-term plasticity in the cortical GABAergic interneurons” and discuss our research team's contribution to the topic. Indeed, we among other laboratories have demonstrated during the past decade that 1) excitatory glutamatergic synapses targeting the GABAergic interneurons in the hippocampus and the neocortex exhibit various different forms of activity-induced learning-related long-term plasticity (Lamsa et al. 2005; Lamsa et al. 2007a; Lamsa et al. 2007b). Importantly, we have demonstrated that the plasticity forms are often specific to interneuron type; anatomically specialized GABAergic interneurons exhibit distinct long-term plasticity mechanisms and require specific neuronal activity patterns for the plasticity induction (Oren et al. 2009; Nissen et al. 2010). 2) We have shown that the interneuron plasticity reported in acute brain slice preparations also occurs in the intact brain *in vivo*, and that the plasticity regulation *in vivo* brain is complex (Lau et al. 2017). 3) We have proven that common interneuron types exhibiting synaptic long-term plasticity in a rodent brain show plasticity in the human neocortex although with specific features. 4) Both in the rodent and in the human cortex, the interneuron plasticity strongly modifies the local neuronal network activities permanently changing signal transmission through polysynaptic circuits (Lamsa et al. 2005; Szegedi et al. 2016; Szegedi et al. 2017). In addition, our results indicate that interneuron plasticity is required to maintain high temporal precision of principal cells' signal processing in the cortex in the face of learning (Kullmann and Lamsa 2007; Kullmann and Lamsa 2011b).

Introduction

Salient and contextual information in the brain is encoded in firing of neurons as neuronal ensembles, and GABAergic (γ -aminobutyric acid -releasing) inhibitory interneurons play a pivotal role in this process. The activated neuronal ensembles (often referred to as engrams) are thought to represent means carrying relevant stored pieces of information, and they are promptly re-organized by learning (Tonegawa et al., 2015; Poo et al., 2016; Buzsaki and Llinas, 2017). The re-organisation of engrams is at least partly manifested by long-term synaptic plasticity between the excitatory glutamatergic pyramidal neurons (Lisman, 2017). However,

it has been poorly understood whether and how long-term plasticity in GABAergic inhibitory interneurons contributes to this process (McBain et al., 1999; Kullmann and Lamsa, 2011b). It is well established that glutamatergic excitatory neurons exhibit synaptic and non-synaptic long-term plasticity forms. In contrast, the GABAergic inhibitory neurons were initially considered rigid and unchangeable with a hypothesis that their function may not exhibit learning-associated permanent changes (McBain and Maccaferri, 1997; McBain et al., 1999; Ross and Soltesz, 2001). Yet, a past decade in the research of neocortical and hippocampal microcircuits has revealed sophisticated plasticity forms in synapses to the GABAergic inhibitory neurons (Kullmann and Lamsa, 2011a). Several research groups including ours have independently demonstrated that the GABAergic neurons undergo a wide range of synaptic and non-synaptic activity-induced plasticity processes (Laezza et al., 1999; Alle et al., 2001; Perez et al., 2001; Lamsa et al., 2005; Pelkey et al., 2005; Lamsa et al., 2007b; Lu et al., 2007; Galvan et al., 2010; Sambandan et al., 2010; Peterfi et al., 2012; Griguoli et al., 2013; Le Roux et al., 2013; Camire and Topolnik, 2014; Zarnadze et al., 2016; Nicholson and Kullmann, 2017). A remarkable feature in their plasticity is – in terms of its induction and expression – that it often (although not always) differs from that known to exist in the excitatory principal neurons (Kullmann and Lamsa, 2007; Pelkey and McBain, 2008; Bartos et al., 2011; Galvan et al., 2011; Kullmann et al., 2012; Topolnik, 2012). This thesis will shortly review the topic and explain how our research team activity has participated to the exciting and timely scientific endeavor of the learning-related cortical GABAergic interneuron plasticity. In four main chapters, I will review current understanding of the synaptic long-term plasticity in the interneurons summarizing (1) its induction and the mechanisms explored *in vitro* slice preparation, and (2) present evidence for the plasticity *in vivo* brain. In following chapters (3 and 4), I will elaborate the topic from the rodents (which are the most commonly used experimental animals in cellular neuroscience research) to the human cortex. This research thesis focuses on the learning-associated plasticity specifically in the excitatory synaptic input to the GABAergic neurons.

Results and discussion

1. GABAergic interneurons exhibit many forms of synaptic plasticity and some are specific to interneuron types

Retrospectively, we can conclude that a large source of disagreement on whether the excitatory synapses onto interneurons undergo long-term plasticity stemmed from the experimental paradigms chosen to elicit plasticity, and from the diversity of GABAergic interneuron types. When initially testing a hypothesis on synaptic long-term potentiation (LTP) and –depression (LTD) in interneurons, it was assumed that the GABAergic neurons would undergo plasticity similar to that is seen in the principal pyramidal cells (for discussion, see McBain and Maccaferri (1997). However, later studies have revealed that many GABAergic interneuron subpopulations (but not all, see for instance Lamsa et al., 2005; Lamsa et al., 2007a; Le Roux et al., 2013) fail to show the classic NMDA (N-methyl-D-aspartate) glutamate receptor-mediated synaptic LTP and LTD occurring in the pyramidal neurons (Kullmann and Lamsa, 2007). Instead, most GABAergic interneurons exhibit the LTP or the LTD with different induction mechanisms that require activation of metabotropic glutamate receptors (mGluRs), calcium-permeable α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid -glutamate receptors (CP-AMPA) or voltage-gated calcium channels (Galvan et al., 2011; Kullmann and Lamsa, 2011b; Pelkey et al., 2017).

Another important reason explaining why no consensus existed for a long time with the interneuron plasticity results (see McBain and Maccaferri, 1997; Kullmann and Lamsa, 2011b) is the diversity of cortical GABAergic interneuron types (Ascoli et al., 2008; Klausberger and Somogyi, 2008). Cortical GABAergic neurons are currently classified into at least five different major subclasses whose specific features already emerge during early ontogenic development (for a review, see Pelkey et al., 2017). Thus, the pioneering studies examining synaptic plasticity in the GABAergic cortical neurons expected the interneurons to behave in this regard as a relatively homogenous group, akin to what had been observed with the principal neurons (Buzsaki and Eidelberg, 1982; Maccaferri and McBain, 1996; McMahon and Kauer, 1997; Cowan et al., 1998; Mahanty and Sah, 1998). Yet, later it was demonstrated that distinct interneuron subpopulations as well as different afferent pathways to an individual interneuron can strongly differ in their plasticity features (Lei and McBain, 2004; Lamsa et al., 2005; Nissen et al., 2010; Sambandan et al., 2010; Le Roux et al., 2013; Galvan et al., 2015; Zarnadze et al., 2016). Consequently, various early attempts to address the question whether the synaptic long-term potentiation exists in the GABAergic cells produced variable and

inconclusive results (for a review see McBain and Maccaferri 1997). As more recent studies have shown, it is crucial that the cortical interneurons are tested for the hypothesis as distinct subgroups rather than as an entity (Lei and McBain, 2004; Kullmann and Lamsa, 2011b; Le Roux et al., 2013).

Work from many laboratories, including seminal work of prof. Peter Somogyi in the University of Oxford (UK), has demonstrated that hippocampal GABAergic interneurons represent various specialized cell types (Somogyi and Klausberger, 2005). Consequently, in the hippocampal CA1 area (field 1 in hippocampal area named as *Cornu Ammonis*) alone there are roughly twenty different GABAergic interneuron types (Klausberger and Somogyi, 2008). The hippocampus with its clearly identified GABAergic cell types allowed us to test a hypothesis whether synaptic long-term plasticity in interneurons was actually cell-type specific. Our results at least partly explained the previously inconsistent outcome of the interneuron plasticity experiments.

In 2005, we published a research article with prof. Dimitri Kullmann (University College London, UK) demonstrating that the hippocampus shows a clear spatial pattern for one specific type of LTP (NMDAR-dependent) among the CA1 area interneurons (Lamsa et al., 2005).

We discovered that when using an associative pre- and postsynaptic discharge pairing protocol (identical to what is commonly used for LTP induction in pyramidal cells), less than half of the tested postsynaptic GABAergic cells showed LTP, while a majority failed to show plasticity. We reported these findings in two separate articles published in *Nature Neuroscience* (Lamsa et al., 2005) and *The Journal of Physiology* (Lamsa et al., 2007a), the former describing the phenomenon in interneurons and the latter uncovering its induction mechanism downstream to the NMDAR activation (which we found is different from that existing in pyramidal cells, since in the interneurons a beta isoform of Ca^{2+} /calmodulin-dependent protein kinase II -enzyme is required for LTP, whereas in the CA1 pyramidal cells alpha isoform is necessary for the long-term potentiation).

The bimodal expression pattern of the NMDAR-mediated LTP among the CA1 area interneurons encouraged us to approach an anatomy specialist, prof. Somogyi, and suggest a collaboration project to test whether the plasticity in hippocampal interneurons is associated with anatomically specialized interneuron types. We set a simple hypothesis: testing two common LTP induction protocols, we investigated whether there is a correlation between the plasticity result and an identified postsynaptic interneurons type? This required rigorous *post hoc* anatomical and immunohistochemical analyses of the electrophysiologically investigated postsynaptic neurons. We first focused on the hippocampal O-LM interneuron type (named as *Oriens-Lacunosum Moleculare* interneuron because its axon characteristically occupies these layers) (McBain et al., 1994) in the CA1 area to test this idea. The O-LM cell was a good candidate to study this question, because there was already evidence in the literature showing that LTP often occurs in interneurons with soma in *stratum oriens* layer of the CA1 area (Perez et al., 2001). The O-LM interneuron somata locate in *stratum oriens*. Indeed, we were able to demonstrate that the O-LM cells consistently show LTP, which is addition was mechanistically different from the LTP in pyramidal cells. We published these findings in two research articles first showing the novel type of LTP occurring in many CA1 area interneurons (but not in pyramidal cells) and then demonstrating that it requires the activation of postsynaptic calcium-permeable AMPA receptors and group I metabotropic glutamate receptors (Lamsa et al., 2007b).

In addition, we demonstrated in the articles that the synapses to interneurons with this type of LTP do not show the conventional "pyramidal cell-like LTP" that requires the glutamatergic NMDA receptors. The second research article published in *The Journal of Neuroscience* (Oren et al., 2009), was released two years later when I already had moved to Oxford University as an independent research group leader. In that paper we further demonstrated that the O-LM cells consistently exhibit the CP-AMPA-dependent LTP form.

Both these studies utilized a technically challenging experimental approach – a sequential recording from a postsynaptic interneuron with two separate micropipettes – in which the postsynaptic cell was first recorded using a perforated patch -method to minimize dilution of the intracellular contents. It was crucial for stable long-lasting recordings that allowed testing subsequent plasticity protocols in the same neuron. For anatomical identification of

postsynaptic cell type, the recorded neurons were re-patched with a conventional whole-cell micropipette, and the cells were filled with a marker molecule (neurobiotin or biocytin) for their *post hoc* visualization. The results played a key role in our review article published the same year in *Nature Reviews Neuroscience* (Kullmann and Lamsa, 2007).

This project generated two further research articles both released in *The Journal of Neuroscience* and published with Prof. Somogyi while I was in Oxford. We showed that the CP-AMPA-dependent LTP occurs not only in O-LM cells but in addition in other neurons expressing parvalbumin (PV) (note: some O-LM cells also exhibit this marker although weakly, see Ferraguti et al., 2004), more specifically basket cells and in axo-axonic cells, and in interneurons with no PV but with neuronal nitric acid synthase (nNOS) (Nissen et al., 2010; Szabo et al., 2012). On the contrary, this plasticity was absent in the CA1 area interneurons expressing cholecystinin (CCK) but not PV (Nissen et al., 2010). In addition, we demonstrated that the O-LM cells and the nNOS-expressing ivy cells both exhibit CP-AMPARs and the CP-AMPA-dependent LTP because they lack the glutamate AMPA receptor subunit 2 (GluA2) (Szabo et al., 2012). Interestingly, later studies have revealed that interneuron types with CP-AMPARs are mostly derived from the same developmental brain area during early ontogenesis (Akgul and McBain, 2016). Hence, we speculate that the specific type of plasticity is already programmed in the interneurons during early ontogenesis.

2. Identified interneuron types show the learning-related long-term plasticity *in vivo*

Although *in vitro* slice preparation studies enabled the detailed investigation of interneuron plasticity mechanisms in many identified cell types – because the method easily allows long and stable recording from identified cells – it still remained open whether the same cell types would similarly show plasticity in the intact brain of a living animal. Interestingly, some publications already existed showing indirect evidence for the activity-induced long-term potentiation and -depression in interneurons of the hippocampal CA1 area (Buzsaki and Eidelberg, 1982; Dupret et al., 2013). In these articles, which utilized extracellular recording of spiking activity of unidentified CA1 area interneurons, it was demonstrated that spike coupling of the presynaptic pyramidal cells (or their fibers) and the interneurons in a rat hippocampus was permanently strengthened or weakened by either a common LTP-induction

paradigm (applying repetitive extracellular electrical stimulation, see Buzsaki and Eidelberg, 1982) or following spatial learning tasks (Dupret et al., 2013). However, neither of these studies did or was able to identify the postsynaptic interneuron types for methodological reasons.

Hence, we next investigated the long-term plasticity of synaptic excitatory drive of anatomically identified CA1 area interneurons *in vivo*. To optimize long-term stability of the recordings, the rats were anaesthetized during experiments (by combination of urethane, xylazine and ketamine). Rather than using a multichannel electrode (Dupret et al., 2013), we studied the interneuron spiking probability with an extracellularly juxtapositioned glass micropipette in response to microelectrode stimulation of afferent glutamatergic projection fibers. The juxtacellular glass microelectrode recording method allowed us to label the studied cells with neurobiotin for *post hoc* anatomical analyses and identify interneuron type (Lau et al., 2017). We focused the study on the postsynaptic fast-spiking PV+ basket cells and the non fast-spiking nNOS+ (immunopositive for neuronal nitric oxide synthase) ivy cells, which we and others had previously shown in the *in vitro* slice preparation to exhibit robust LTP by the high-frequency stimulation (Alle et al., 2001; Nissen et al., 2010; Szabo et al., 2012; Campanac et al., 2013; Le Roux et al., 2013).

Similar to the results by Dupret et al. (2013) as well as Buzsaki and Eidelberg (1982), we found that the fast-spiking CA1 interneurons can generate either LTP or LTD following high-frequency glutamatergic fiber activity. Interestingly, when identifying the interneuron types we found that both the PV+ basket cells as well as the ivy cells could generate either LTP or LTD in these conditions. Because the results differed from what we had previously observed in slice preparations (*in vitro* the LTP was consistently generated in both of these CA1 interneuron types), we hypothesized that the direction of plasticity *in vivo* might be regulated by the underlying brains state in the anaesthetized animal defined by the local field potential oscillation pattern at the time when the plasticity was induced (see Kullmann and Lamsa, 2007). However, we found that neither did the occurrence of predominant theta (4-8 Hz) oscillation or slow wave (1 Hz) activity manage to explain whether the LTP or the LTD was generated in these interneurons (Lau et al., 2017).

Hence, we suggested that the complex plasticity results *in vivo* could possibly emerge from variable underlying modulatory effects of monoaminergic, cholinergic or endocannabinoid system in the experiments. Indeed, such modulations have been reported with pharmacological agents in slice preparations (Peterfi et al., 2012; Griguoli et al., 2013), and in intact brain such effects could be generated endogenously. Our results *in vivo* rat hippocampus were first reported in *Brain Structure and Function* (Lau et al., 2017).

3. Human cortical microcircuits show evolutionarily conserved interneuron plasticity with specific features

We asked whether the interneuron plasticity reported in the rodent occurs similarly in the human brain, or if there are specific plasticity features in the human cortex not present in a rat or mice? The question is highly relevant, since recent studies have demonstrated that the human neocortical microcircuits are not identical to rodents but show various specializations in the intrinsic neuronal and synaptic functions (Molnar et al., 2008; Blazquez-Llorca et al., 2010; Defelipe, 2011; Testa-Silva et al., 2014; Eyal et al., 2016; Molnar et al., 2016; Sousa et al., 2017). Many of these adaptations are either enhancing the temporal signal processing or the spatial propagation of neuronal activity in the human neocortex. There is an emerging idea that some of these features may have evolved during the human evolution to enhance the brain computational power (DeFelipe et al., 2002; Lourenco and Bacci, 2017; Sousa et al., 2017). However, it had remained unknown whether the plasticity of GABAergic inhibitory circuits also showed specific functional features in the human cortex.

We investigated the question in acute slices prepared from neocortical tissue samples resected in a deep brain oncology or aneurism surgery in order to have the access to subcortical pathological target (Molnar et al., 2008; Szegedi et al., 2017). Such samples represent the closest to healthy control tissue, since the patients are typically operated with a short delay from the first symptoms and they lack systematic and persistent pre-medication (unlike the epilepsy patients) (Lourenco and Bacci, 2017). Importantly, the resected neocortical tissue samples in the operations locate far from the pathological target. For clarity, we have systematically reported in our studies the operated patient age, gender and

their primary clinical diagnosis leading to the operation (Szegegi et al., 2016; Szegegi et al., 2017).

Whole-cell recordings from the layer 2-3 PV+ basket cells revealed a robust LTD in their glutamatergic afferents by the high-frequency bursting of the fibers. The LTD was similarly generated by extracellular stimulation in a rat and in the human (Szegegi et al. 2016). In both cases, the LTD showed presynaptic expression site and it was blocked by antagonist of the group I metabotropic glutamate receptors. The results are well in line with previous reports in rodents (Yazaki-Sugiyama et al., 2009) showing that metabotropic receptors mediate the LTD in the fast-spiking cortical interneurons (Lu et al., 2007; Peterfi et al., 2012).

Yet, about 15 % of pyramidal cell to fast-spiking interneuron connections in the human neocortex layer 2-3 exhibit very large monosynaptic glutamatergic EPSPs (VLEs, average amplitude 13 mV) elicited by single pyramidal cell spike (Molnar et al., 2008; Komlosi et al., 2012; Szegegi et al., 2016; Szegegi et al., 2017). The VLEs are often suprathreshold hence representing a microcircuit feature not occurring in a rat and being possibly specific to the human neocortex (Molnar et al., 2016). Importantly, we found that the strong synaptic VLE-connections are able to trigger the mGluR-dependent LTD independently; a high frequency bursting activity of just single pyramidal cell triggers the LTD, which in a rat required simultaneous co-activation of multiple glutamatergic fibers. In our research article published in *PLoS Biology*, we speculated that the VLE synapses – with their multivesicular glutamate release (Molnar et al., 2016) – may be sufficient to activate perisynaptic mGluRs critical for the LTD in postsynaptic PV+ cells. In the rat neocortex the mGluR activation requires spill-over glutamate released from several simultaneously active adjacent synapses (Rusakov et al., 1999).

Altogether, we found that similar plasticity – in terms of its induction by the high-frequency afferent fiber bursting and the pharmacological sensitivity – is induced in a rat and in the human neocortex glutamatergic synapses to PV+ basket cells. However, the strong VLE connections between two individual neurons in the human can trigger the plasticity independently. The results suggest an evolutionarily conserved mechanism for the

interneuron plasticity in the mammalian neocortex, but reveal microcircuit level specializations between the species in the learning-related interneuron plasticity.

4. Interneuron long-term plasticity produces permanent changes in local network activity both in the rodent and in the human

Since GABAergic interneurons play a pivotal role in organizing the space and the time of cortical ensemble activity (see Introduction), we finally investigated whether the interneuron plasticity was sufficient to alter the activity in neuronal networks. First, we investigated this in the rodent hippocampus inducing the long-term plasticity in the CA1 area circuitry so that LTP was either restricted to postsynaptic pyramidal cells, or that it in parallel also occurred in the GABAergic interneurons.

We demonstrated LTP in both the pyramidal cells and in the disynaptic GABAergic inhibition (i.e. LTP in interneurons) is required to preserve the high temporal fidelity of the CA1 pyramidal cells' input-output transformation (meaning the temporal accuracy how synaptic inputs from the CA3 area are integrated in the CA1 cells to generate their action potential firing) following CA3 area high-frequency bursting (Lamsa et al., 2005). In other words, we demonstrated that LTP in GABAergic interneurons is needed to preserve fast co-incidence detection in the excitatory signal transmission from the CA3 to CA1 area in the face of learning and LTP in pyramidal neurons. The results stress the importance of GABAergic interneuron long-term plasticity during hippocampal learning processes.

Correspondingly, in the human neocortex the layer 2-3 single pyramidal cell spike –evoked network activity (called complex events or the ensembles) allowed us to test if the plasticity in pyramidal cell-to-interneuron synapses was able to modify the evoked network activity. Indeed, we found that in parallel with the mGluR-dependent LTD in the fast-spiking PV+ basket cells, there was a change in the complex event pattern evoked; the PV+ basket cells, which are characteristically activated at the earliest phase of the complex events (Szegedi et al., 2017), were silenced in the evoked ensembles by the mGluR-dependent LTD (Szegedi et al., 2016). These results show that also in human neocortex the long-term plasticity in PV+

interneurons leaves a permanent imprint in the network activity pattern evoked in the local circuitry.

Conclusions

Various laboratories during the past decade have shown that learning-related and activity-induced long term plasticity occurs not only in the cortical pyramidal cells but in addition in the GABAergic inhibitory interneurons. Our laboratory has contributed to this endeavor showing that glutamatergic excitatory fibers undergo long-term plasticity in specialized anatomically identified cortical interneuron types in a rodent as well as in the human. We have demonstrated that same cell types that exhibit the plasticity *in vitro* slice preparations, do also show LTP and LTD *in vivo* rodent brain. Importantly, in these interneurons the cellular mechanisms and the induction pattern of LTP often differ from that known in pyramidal cells. The interneuron-specific plasticity mechanisms may reflect their different physiological firing pattern in learning processes, such as in the hippocampus during spatial learning tasks (Klausberger and Somogyi, 2008).

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Annexes

1. Author contributions in the publications

i. Hebbian LTP in feed-forward inhibitory interneurons and the temporal fidelity of input discrimination. **Lamsa K**, Heeroma JH, Kullmann DM. *Nat Neurosci.* 2005. (7):916-24.

K.L. performed electrophysiological experiments and analyses, J.H.H. performed anatomical experiments and analyses, and K.L., J.H.H. and D.M.K. designed the study and wrote the manuscript. Supervision D.M.K.

ii. Anti-Hebbian long-term potentiation in the hippocampal feedback inhibitory circuit **Lamsa K**, Heeroma JH, Somogyi P, Rusakov DA, Kullmann DM. *Science.* 2007. 315(5816):1262-6.

K.L. performed electrophysiological experiments and analyses, J.H.H. and P.S. performed anatomical experiments and analyses, and K.L., J.H.H., D.A.R. and D.M.K. designed the study and wrote the manuscript. Supervision D.M.K.

iii. Cell type-specific long-term plasticity at glutamatergic synapses onto hippocampal interneurons expressing either parvalbumin or CB1 cannabinoid receptor. Nissen W, Szabo A, Somogyi J, Somogyi P, **Lamsa K**. *The Journal of Neuroscience.* 2010. 30:1337-1347.

W.N. and K.L. performed electrophysiological experiments and analyses, A.S., J.S. and P.S. performed anatomical experiments and analyses. W.N. and K.L. designed the study and wrote the manuscript. Supervision K.L.

iv. Long-term plasticity in identified hippocampal GABAergic interneurons in the CA1 area in vivo. Lau PY, Katona L, Saghy P, Newton K, Somogyi P, **Lamsa K**. *Brain Struct Funct.* 2017. 222(4):1809-1827.

P.Y.L. and L.K. performed electrophysiological experiments and analyses. S.P. K.N. and P.S. performed anatomical experiments and analyses. K.L. designed the study, and K.L. and P.S. wrote the manuscript. Supervision K.L.

v. Plasticity in Single Axon Glutamatergic Connection to GABAergic Interneurons Regulates Complex Events in the Human Neocortex. Szegedi V, Paizs M, Csakvari E, Molnar G, Barzo P, Tamas G, **Lamsa K**. *PLoS Biol.* 2016. 9;14(11):e2000237.

Conceptualization K.L., data curation K.L., electrophysiological experiments V.S., G.M. and K.L.,

anatomical experiments M.P., E.C. and K.L. Data analyses V.S., M.P., E.C., G.M. and K.L. Resources P.B., G.T. and K.L. Supervision and writing original manuscript K.L. Reviewing and editing the manuscript GM., G.T. and K.L.