Petilla 2005: Nomenclature of features of GABAergic interneurons of the cerebral cortex

Alonso-Nanclares L., Anderson S., Ascoli G., Benavides-Piccione R., Burkhalter A., Buzsaki G., Cauli B., DeFelipe J., Fairen A., Feldmeyer D., Fishel G., Fregnac Y., Freund T.F., Fukuyi K., Galarreta M., Goldberg J., Helmstaedter M., Hensch T., Hestrin S., Kisvarday Z., Lambolez B., Lewis D., McBain C., Marin O., Markram H., Monyer H., Muñoz, A., Petersen C., Rockland K., Rossier J., Rudy B., Somogyi P., Staiger J.F., Tamas G., Thomson A., Toledo-Rodriguez M., Wang X-J., Wang Y., West D. and Yuste R.

The GABAergic interneurons of the cerebral cortex are a heterogeneous population of cells which play a key role in the cortical circuit. Their heterogeneity manifests itself in every aspect of their phenotype, in morphological, electrophysiological or molecular studies of these cells. At the same time, it has been long recognized that neocortical interneurons appear to belong to different classes and that the variability in their features within a class appears much smaller than differences among classes. We are convinced that interneuron cell types are indeed real and therefore it is essential to identify these classes in order to achieve an understanding of the circuits in which they operate.

The problem of classifying neocortical interneurons has been a topic of debate for more than a hundred years, yet a satisfactory consensus remains to be reached. There has been generation after generation of excellent work in the study of these cells. However, the nomenclature used to describe different features of these neurons and the classification criteria is often idiosyncratic and sometimes even arbitrary, as it varies from research group to research group and even among investigators working in the same laboratory. As a consequence, communication among investigators as to what type of interneuron they study and how their research relates to studies carried out elsewhere on similar cells is difficult. Our effort in this document is to streamline the nomenclature of interneuron properties in order to facilitate the exchange of information between researchers, to aid ongoing efforts to define a classification of these cells, and to help build a foundation for future progress in the field.

Cortical interneurons have been characterized using morphological, molecular and physiological features. Ideally, the characterization of a neuron would be complete when information regarding all these three criteria is considered. At the same time, neurons do not have a separate morphology, physiology or molecular biology, these are features of their multidimensional existence created by detection methods. Each investigator may choose a particular method to characterize a cell, but it should not be forgotten that there is only one unitary reality behind it all.

What follows is our proposal to standardize the nomenclature of different features of neocortical interneurons. It arose out of a recent meeting devoted to this topic in Ramón y Cajal's birthplace, Petilla de Aragón (Navarra, Spain) and is rooted in the collective work performed over the years in many laboratories. Rather than imposing a classification, as a first step we seek to standardize the nomenclature by which researchers label different features of the interneurons. We seek to agree upon a series of clear and common terms used by all researchers that could constitute a list of the essential features that differentiate interneurons. We encourage investigators to use the same terms to describe the same features which will help to capitalize and profit from our combined effort.

With this document, we co-authors propose and publicly endorse a set of clear-cut and practical terms and criteria. We hope that this reference will be adopted and used by all investigators to label and classify the interneurons they encounter. The idea is that this first step, generating and agreeing upon a unified method for characterizing GABAergic interneurons, will then later lead to a classification adopted by investigators of the neocortex.

Finally, this nomenclature proposal is just a reflection of the state of our field in 2005. Our group has also created a scientific committee that will update this nomenclature as needed and seek a uniform classification. Continuous feedback, constructive criticism, and suggestions are invited from the whole scientific community (committee membership and contact information below). This current document should only be viewed as an initial effort, a stepping-stone towards an increasingly more accurate and useful nomenclature that can pave the way for a future classification of neuron types of the cerebral cortex.

Standardized Nomenclature of Interneuron Features

- What follows is a standardized set of features and terms that can be used to characterize neocortical GABAergic interneurons. It is not a method to code the cells, but to describe them in a way that is understood by most investigators. The terms are numbered for easy reference.
- The term "interneuron" is applied throughout, irrespective whether the axon of the cell leaves the cortical area where the cell body is located, because the accepted general use of the term helps communication.
- While our focus is on GABAergic interneurons of the cerebral cortex, this set of features and terms may be applicable or at least adaptable to broader and/or different neuronal classes.
- These terms are a set of labels which are not exclusive. Therefore more than one label from each category can be applied in many cases to describe a given neuron.
- Terms are not listed in order of importance.
- These terms are meant as guidelines to enhance communication, not as criteria with which to evaluate research. We intend that these terms will be used constructively, not destructively, to advance all research on interneurons.
- These labels are not meant as a classification of interneuron subtypes.
- Investigators are strongly encouraged to specify contextual data (species, strain, age, gender, layer, sublayer, cortical area, experimental method, type of stimulation, temperature, etc.) to help others put their descriptions in the proper framework.
- Every effort should be made by researchers to be quantitative in their description, so that their characterization can be objectively compared with that of other researchers.

I. Morphological features

1. Soma
    - 1.1 Shape
        - 1.1a Round
        - 1.1b Fusiform
        - 1.1c Triangular
        - 1.1d Polygonal
        - 1.1e Other
    - 1.2 Size (quantify)
    - 1.3 Orientation
        - 1.3a Radial
        - 1.3b Tangential

- 2. Dendrite
    - 2.1 Dendrite arbor topology
        - 2.1a Unipolar
        - 2.1b Bidirectional (radial/tangential)
            - 2.1b1 Bitufted: Two tufts in opposite directions.
            - 2.1b2 Bipolar: Two long primary dendrites in opposite directions.
        - 2.1c Multipolar: Three or more primary dendrites in multiple directions.
        - 2.1d With single “apical-like”/ “pyramidal-like” thick, tapering projection in any direction
        - 2.1e Other
    - 2.2 Branch metrics (label dendritic branches in a hierarchical fashion)
        - 2.2a Frequency and number
        - 2.2b Angle (e.g. amplitude, planarity)
        - 2.2c Taper
        - 2.2d Tortuosity
        - 2.2e Size (e.g. number, length, diameter)
        - 2.2f Length
        - 2.2g Number of nodes
        - 2.2h Number of endings
        - 2.2i Sholl analysis
        - 2.2j Fractal analysis
    - 2.3 Fine structure
        - 2.3a Spines (number, size and distributions)
        - 2.3b Beads (number, size and distributions)
    - 2.3 Morphology of synaptic inputs
        - 2.3a Density
        - 2.3b Symmetric/Asymmetric (Type I vs. Type II)
        - 2.3c Location (where on dendrite- and/or elsewhere)
        - 2.3d Origin (afferent pathway/presynaptic neuron)
- 3. Axon
    - 3.1 Initial Segment (before 1st bifurcation)
        - 3.1a. Origin
            - 3.1a1 Soma
            - 3.1a2 Dendrite
        - 3.1b. Course
            - 3.1b1 Deep/Superficial (Ascending/Descending)
            - 3.1b2 Radial/Tangential
    - 3.2 Arbor
        - 3.2a. Unmyelinated/Myelinated
        - 3.2b Ascending/Descending
        - 3.2c Radial/Tangential
        - 3.2d Intra/interlaminar
            - 3.2d1 Ascending/descending
        - 3.2e Intra/inter columnar
        - 3.2f Density (quantify)
        - 3.2g Branching metrics

        - 3.2g1 Frequency or number
        - 3.2g2 Angles
        - 3.2g3 Tortuosity
        - 3.2g4 Branch length
        - 3.2g5 Other
    - 3.2h Pattern of axonal arborization
        - 3.2h1 Dense plexus of highly branched axons
        - 3.2h2 Recurrent arches
            - Ascending/descending (willows)
        - 3.2h3 Long, horizontal branches with clustered terminal arbors (horsetail)
- 3.3 Terminal branch properties
    - 3.3a Curved
        - 3.3a1 Basket terminals (curved preterminal branches)
    - 3.3b Straight
    - 3.3c Clustered
        - 3.3c1 Chandeliers (also straight)
- 3.4 Boutons
    - 3.4a Density
    - 3.4b Structure
        - 3.4b1 Terminal/En passant
        - 3.4b2 Axonal stalks
    - 3.4c Clustering pattern
    - 3.4d Size
    - 3.4e Ultrastructure
        - 3.4e1 Density/Type of Vesicles
        - 3.4e2 Type of synapse
        - 3.4e3 Density of mitochondria
- 3.5 Postsynaptic targets (specify predicted/putative vs. identified/confirmed)
    - 3.5a Pyramidal cells
        - 3.5a1 Pyramidal location
            - 3.5a1a Pyramid Soma/Proximal dendrite
            - 3.5a1b Apical main dendrite
            - 3.5a1c Apical oblique dendrite
        - 3.5a2 Tuft
        - 3.5a3 Basal dendrite
        - 3.5a4 Axon initial segment
    - 3.5b Interneuron
        - 3.5b1 Soma/proximal dendrite
        - 3.5b2 Distal dendrite
        - 3.5b3 Axon
    - 3.5c Spine/Shaft (ratio)
    - 3.5d Other
        - e.g. Vascular system, glia
- 3.6 Pattern on postsynaptic target
    - 3.6a Clustered

        - 3.6b Distributed
        - 3.6c Gradient
- 4. Gap Junctions
    - 4.1 Source
        - 4.1a Soma
        - 4.1b Dendrite
        - 4.1c Axon
    - 4.2 Target
        - 4.2a Location and distribution
            - 4.2a1 Dendrite/Axon
            - 4.2a2 Proximal/Distal
            - 4.2a3 Density/Probability (number)

II. Molecular features

1. Molecular composition of the cell. Here we only highlight those genes whose importance to interneuron identity is well established, but we recognize this list is extremely expandable.

    - 11 Transcription factors (e.g. Nkx2.1, Dlx1, Dlx2, Lhx6, NPAS1, NPAS3, Vax1)
    - 1.2 Neurotransmitters or their synthesizing enzymes (+/-)
      (e.g. GABA, GAD,NO, nNOS, TH, ACh, ChAT)
    - 1.3 Neuropeptides (+/-)
      (e.g. SOM, VIP, NPY, CCK, TK)
    - 1.4 Calcium binding proteins (+/-)
      (e.g. PV, CR, CB)
    - 1.5 Receptors
        - 1.5a Ionotropic
          (e.g. GluR1-7, NMDAR1, $GABA_A$, Nicotinic)
        - 1.5b Metabotropic
          (e.g. GABAergic, glutamatergic, muscarinic, serotonergic, noradrenergic, histaminergic, dopaminergic, cannabinoid)
    - 1.6 Structural proteins
    - 1.7 Cell surface markers (+/-)
      (e.g. VVA (*Vicia villosa* agglutinin), SBA (soybean agglutinin))
    - 1.8 Ion channels expression (+/-)
      (e.g. Kv3.1, Kv3.2, Ih (HCN1-4), I_T (T type current), Ca α1, Cα3.1-3, Kv1.1, Kv4.2 or Kv4.3, Kv2.1, Kv2.2, SK and BK, KCNQ)
    - 1.9 Connexins
    - 1.10 Transporters
        - 1.10.a Plasma membrane
        - 1.10.b Vesicular
2. Molecular properties of its presynaptic input cell (a similar list as in II. 1)

III. Physiology/biophysical features

1. Passive/subthreshold parameters
    - 1.1 Vm
    - 1.2 Membrane time constant (fast, slow)

- 1.3 Input resistance
- 1.4 Rheobase (minimal amplitude of current stimulation able to cause firing)
- 1.5 Chronaxie (shortest duration of a stimulus twice the rheobase necessary to cause firing)
- 1.6 Rectification
- 1.7 Oscillation (specify frequency)
- 1.8 Resonance

2. AP measurements
    - 2.1 Amplitude, threshold, half-width,
    - 2.2 AHP
    - 2.3 ADP
    - 2.4 Changes in AP waveform during train
    - 2.5 Dendritic backpropagation
3. Depolarizing plateaus (long duration spikes)
4. Firing pattern (specify amplitude and duration of depolarizing current)
    - 4.1 Oscillatory and resonant behavior
    - 4.2 Onset response to somatic depolarizing current step
        - 4.1 Continuous: Onset behavior similar to steady state behavior
        - 4.2 Burst: Smaller ISI at onset than at steady state (doublets or more)
        - 4.3 Delayed (between stimulus onset and first spike)
            - With one spike at onset
        - 4.4 Other
    - 4.3 Steady State response to depolarizing current step
        - 4.3a Amplitude accommodation
        - 4.3b Spike frequency adaptation (with 1 or more time constants)
        - 4.3c Maximal frequency at steady state (saturating frequency)
        - 4.3d Minimal maintained or continuous frequency at steady state
        - 4.3e Slope of I-f curve
        - 4.3f Changes in AHP amplitude (AHP accommodation)
        - 4.3g Slow AHP after current step
        - 4.3h ISI distribution
            - 4.3h1 Irregular spiking (Variable AP discharge/broad ISI distribution)
            - 4.3h2 Stuttering (Interruptions of high frequency firing, mixed frequencies)
        - 4.3i Repetitive bursts/doublets
        - 4.3j Silent (complete absence steady state AP firing)
        - 4.3k Other
5. During hyperpolarizing step
    - 5.1 Rectification
        - 5.1a Onset
        - 5.1b Steady state
        - 5.1c Difference between onset and steady state (sag)
    - 5.2 Rebound
        - 5.2a Hump
        - 5.2b Spike

6. Features of interneuron spiking recorded extracellularly
    6.1 Phase relationship to oscillation
    6.2 Functional response specificity (e.g. receptive field)
    6.3 Cross correlation based identification
    6.4 Other dynamics
7. Post synaptic responses
    7.1 Spontaneous
        1.1a Rise time, amplitude, decay, reversal potential, receptors, frequency, charge
    7.2 Evoked
        1.2a Rise time, amplitude, decay, reversal potential, receptors, charge
        1.2b Release probability
    7.3 Ratio of receptor subtypes of combined synaptic current
    7.4 Spatial and temporal summation
    7.5 Gap junctions (describe the coupled cell)
        1.5a Coupling coefficient, rectification
    7.6 Short-term plasticity
        1.6a Kinetics of facilitation, depression, synaptic augmentation, and post-tetanic potentiation
    7.7 Long-term plasticity (of initial and steady state response)
        1.7a Kinetics, polarity, charge and amplitude

Petilla 2005 Co-authors:

Name	**Affiliation**	**Email Address**
Alonso-Nanclares, Lidia	Cajal Institute	aidil@cajal.csic.es
Anderson, Stewart	Cornell	saa2007@med.cornell.edu
Ascoli, Giorgio	SFN-George Mason	ascoli@gmu.edu
Benavides-Piccione, Ruth	Cajal Institute	rbp@cajal.csic.es
Burkhalter, Andreas	Washington University	burkhala@pcg.wustl.edu
Buzsaki, Giuri	Rutgers University	buzsaki@axon.rutgers.edu
Cauli, Bruno	ESPCI, Paris	bruno.cauli@espci.fr
DeFelipe, Javier	Cajal Institute	defelipe@cajal.csic.es
Fairen, Alfonso	Alicante	fairen@umh.es
Feldmeyer, Dirk	Juelich	d.feldmeyer@fz-juelich.de
Fishel, Gordon	NYU	fishell@saturn.med.nyu.edu
Fregnac, Yves	UNIC-CNRS	fregnac@iaf.cnrs-gif.fr
Freund, Tamas F.	Hungarian Academy	freund@koki.hu
Fukuyi, Karube	University of Debrecen	fuyuki@chondron.anat.dote.hu
Galarreta, Mario	Stanford	galarreta@stanford.edu
Goldberg, Jesse	MIT	jesseg1@MIT.EDU
Helmstaedter, Moritz	MPI Heidelberg	Moritz.Helmstaedter@mpimf-heidelberg.mpg.de
Hensch, Takao	Riken, Tokyo	hensch@riken.jp
Hestrin, Shaul	Stanford	shaul.hestrin@stanford.edu
Kisvarday, Zoltan	University of Debrecen	kisvarday@chondron.anat.dote.hu
Lambolez, Bertrand	ESPCI, Paris	Bertrand.Lambolez@espci.fr
Lewis, David	University of Pittsburgh	lewisda@upmc.edu
McBain, Chris	NINDS	mcbainc@mail.nih.gov
Marin, Oscar	Alicante	o.marin@umh.es
Markram, Henry	EPFL	henry.markram@epfl.ch
Monyer, Hannah	Heidelberg	hm2221@columbia.edu
Muñoz, Alberto	Cajal Institute	amunozc@bio.ucm.es
Petersen, Carl	EPFL	carl.petersen@epfl.ch
Rockland, Kathy	Riken, Tokyo	rockland@brain.riken.go.jp
Rossier, Jean	ESPCI, Paris	jean.rossier@espci.fr
Rudy, Bernardo	NYU	rudyb01@endeavor.med.nyu.edu
Somogyi, Peter	MRC Oxford	peter.somogyi@pharm.ox.ac.uk
Staiger, Jochen F.	Heinrich-Heine-University	jochen@hirn.uni-duesseldorf.de
Tamas, Gabor	University Szeged	gtamas@bio.u-szeged.hu
Thomson, Alex	London University	alex.thomson@ulsop.ac.uk
Toledo-Rodriguez, Maria	EPFL	maria.toledo@epfl.ch
Wang, Xiao-Jing	Brandeis	xjwang@brandeis.edu
Wang, Yun	Tufts University	yun.wang@tufts.edu
West, David	London University	david.west@ulsop.ac.uk
Yuste, Rafael	Columbia University	rmy5@columbia.edu

Petilla Classification Committee:

Name	**Affiliation**	**Email Address**
Anderson, Stewart	Cornell	saa2007@med.cornell.edu
Ascoli, Giorgio	SFN-George Mason	ascoli@gmu.edu
Burkhalter, Andreas	Washington University	burkhala@pcg.wustl.edu
Buzsaki, Giuri	Rutgers University	buzsaki@axon.rutgers.edu
DeFelipe, Javier	Cajal Institute	defelipe@cajal.csic.es
Markram, Henry	EPFL	henry.markram@epfl.ch
Tamas, Gabor	University Szeged	gtamas@bio.u-szeged.hu