

thalamocortical connections On variability in the density of corticocortical and

Jack W. Scannell, Simon Grant, Bertram R. Payne and Roland Baddeley

doi: 10.1098/rstb.2000.0547 Phil. Trans. R. Soc. Lond. B 2000 **355**, 21-35

Email alerting service Receive free email alerts when new articles cite
top right-hand corner of the article or click **[here](http://rstb.royalsocietypublishing.org/cgi/alerts/ctalert?alertType=citedby&addAlert=cited_by&saveAlert=no&cited_by_criteria_resid=royptb;355/1393/21&return_type=article&return_url=http://rstb.royalsocietypublishing.org/content/355/1393/21.full.pdf)** Receive free email alerts when new articles cite this article - sign up in the box at the

THE ROYAL

BIOLOGICAL
SCIENCES

PHILOSOPHICAL
TRANSACTIONS 능

To subscribe to Phil. Trans. R. Soc. Lond. B go to: **<http://rstb.royalsocietypublishing.org/subscriptions>**

BIOLOGICA SCIENCES

THE ROYAL

PHILOSOPHICAL
TRANSACTIONS ð

ON VARIAT SOCIETY
 On variability in the density of corticocortical and thalamocortical connections
and thalamocortical connections

Jack W. Scannell¹, Simon Grant², Bertram R. Payne³ and Roland Baddeley⁴

Neural Systems Group, Department of Psychology, University of Newcastle uponTyne, Ridley Building, Newcastle uponTyne NE17RU, UK
 (j.w.scannell@ncl.ac.uk)

²Department of Sensorimotor Sytems, Division of Neuroscience (*j.w.scannell@ncl.ac.uk*) *Systems Group, Department of Psychology, University of Newcastle upon Tyne, Ridley Building, Newcastle upon Tyne NE17RU*
(*j.w.scannell* @ncl.ac.uk)
²Department of Sensorimotor Sytems, Division of Neuroscience, Imperial

Fulham Palace Road, LondonW6 8RF, UK ²Department of Sensorimotor Sytems, Division of Neuroscience, Imperial College School of Medicine, Charing Cross Campus,
Fulham Palace Road, London W6 8RF, UK
³Department of Anatomy and Neurobiology, Center for Advance

Fulham Palace Road, London W6 8RF, UK
³Department of Anatomy and Neurobiology, Center for Advanced Biomedical Research, Boston University School of Medicine,
700 Albany Street, Boston, MA 02118, USA ⁴*Department of Experimental Psychology, School of Biological Sciences, University of Sussex, Falmer, Brighton BN1 9RH, UK*

Department of Experimental Psychology, School of Biological Sciences, University of Sussex, Falmer, Brighton BN1 9RH, UK
Variability is an important but neglected aspect of connectional neuroanatomy. The quantitative densi Variability is an important but neglected aspect of connectional neuroanatomy. The quantitative density
of the 'same' corticocortical or thalamocortical connection may vary by over two orders of magnitude
between different Variability is an important but neglected aspect of connectional neuroanatomy. The quantitative density of the 'same' corticocortical or thalamocortical connection may vary by over two orders of magnitude between different between different injections of the same tracer. At present, however, the frequency distribution of connection densities is unknown. Therefore, it is unclear what kind of sampling strategies or statistical between different injections of the same tracer. At present, however, the frequency distribution of connection densities is unknown. Therefore, it is unclear what kind of sampling strategies or statistical methods are appr connection densities is unknown. Therefore, it is unclear what kind of sampling strategies or statistical
methods are appropriate for quantitative studies of connectivity. Nor is it clear if the measured variability
repres methods are appropriate for quantitative studies of connectivity. Nor is it clear if the measured variability
represents differences between subjects, or if it is simply a consequence of intra-individual differences
result represents differences between subjects, or if it is simply a consequence of intra-individual differences
resulting from experimental technique and the exact placement of tracers relative to local spatial and
laminar varia sulting from experimental technique and the exact placement of tracers relative to local spatial and
minar variation in connectivity.
We used quantitative measurements of the density of a large number of corticocortical an

laminar variation in connectivity.
We used quantitative measurements of the density of a large number of corticocortical and thalamo-
cortical connections from our own laboratories and from the literature. Variability in t We used quantitative measurements of the density of a large number of corticocortical and thalamocortical connections from our own laboratories and from the literature. Variability in the density of given corticocortical a cortical connections from our own laboratories and from the literature. Variability in the density of given
corticocortical and thalamocortical connections is high, with the standard deviation of density propor-
tional to corticocortical and thalamocortical connections is high, with the standard deviation of density proportional to the mean. The frequency distribution is close to exponential. Therefore, analysis methods relying on the norma tional to the mean. The frequency distribution is close to exponent
on the normal distribution are not appropriate. We provide an
guidance for samples drawn from exponentially distributed data.
For a given conticocontical For a given corticocortical or thalamocortical connection density, between-individual standard
For a given corticocortical or thalamocortical connection density, between-individual standard
viation is 0.85 to 1.25 times t

guidance for samples drawn from exponentially distributed data.
For a given corticocortical or thalamocortical connection density, between-individual standard
deviation is 0.85 to 1.25 times the within-individual standard For a given corticocortical or thalamocortical connection density, between-individual standard deviation is 0.85 to 1.25 times the within-individual standard deviation. Therefore, much of the variability reported in conve deviation is 0.85 to 1.25 times the within-individual standard deviation. Therefore, much of the variability
reported in conventional neuroanatomical studies (with one tracer deposited per animal) is due to
within-individu reported in conventional neuroanatomical studies (with one tracer deposited per animal) is due to
within-individual factors. We also find that strong, but not weak, corticocortical connections are substan-
tially more vari within-individual factors. We also find that strong, but not weak, corticocortical connections are substantially more variable than thalamocortical connections. We propose that the near exponential distribution of connecti tially more variable than thalamocortical connections. We propose that the near exponential distribution
of connection densities is a simple consequence of 'patchy' connectivity. We anticipate that connection
data will be of connection densities is a simple consequence of 'patchy' connectivity. We anticipate that connection data will be well described by the negative binomial, a class of distribution that applies to events occurring in clum data will be well described by the negative binomial, a class of distribution that applies to events occurring in clumped or patchy substrates. Local patchiness may be a feature of all corticocortical connections and could ring in clumped or patchy substrates. Local patchiness may be a feature of all corticocortical connections
and could explain why strong corticocortical connections are more variable than strong thalamocortical
connections. and could explain why strong corticoc
connections. This idea is supported by
cortical connections in the literature. cortical connections in the literature.
 Keywords: neuroinformatics; anterograde; retrograde; cats; cerebral cortex; thalamus

1. INTRODUCTION

Over the past 100 years, neuroanatomists have exerted a $\sum_{n=1}^{\infty}$
Suppose the past 100 years, neuroanatomists have exerted a
set deal of energy to trace the neural pathways that
in the different regions of the brain. This work has been Wer the past 100 years, neuroanatomists have exerted a
reat deal of energy to trace the neural pathways that
nk different regions of the brain. This work has been
ativated by the belief that an understanding of the reat deal of energy to trace the neural pathways that
ink different regions of the brain. This work has been
intivated by the belief that an understanding of the
innectional structure of the brain will lead to a better nk different regions of the brain. This work has been
otivated by the belief that an understanding of the
onnectional structure of the brain will lead to a better
networking of brain function (Meynert 1890) The notivated by the belief that an understanding of the onnectional structure of the brain will lead to a better nderstanding of brain function (Meynert 1890). The ast century has seen great advances in methods for onnectional structure of the brain will lead to a better
nderstanding of brain function (Meynert 1890). The
ast century has seen great advances in methods for
 $\sum_{i=1}^{\infty}$ connections (e.g. Marchi & Algeri 1895; Nauta nderstanding of brain function (Meynert 1890). The
ast century has seen great advances in methods for
 Ω acing connections (e.g. Marchi & Algeri 1895; Nauta
r Gygax 1954: Kristensson *et al* 1971: Cowan *et al* 1972: ast century has seen great advances in methods for

² racing connections (e.g. Marchi & Algeri 1895; Nauta

² Cygax 1954; Kristensson *et al.* 1971; Cowan *et al.* 1972;

² Arfen & Sawchenko 1984) and in the applicat Check 2. Sawchenko 1984) and in the application of the same space methods to the thalamus and cortex in several t Gygax 1954; Kristensson *et al.* 1971; Cowan *et al.* 1972; Jerfen & Sawchenko 1984) and in the application of nese methods to the thalamus and cortex in several For & Sawchenko 1984) and in the application of
rese methods to the thalamus and cortex in several
pecies (Le Gros Clark 1932, 1942; Rose & Woolsey
948: Polyak 1927–1933) These advances have resulted in nese methods to the thalamus and cortex in several
pecies (Le Gros Clark 1932, 1942; Rose & Woolsey
948; Polyak 1927, 1933). These advances have resulted in

an explosion in our knowledge of brain connectivity (e.g. Zeki & Shipp 1988; Felleman & Van Essen 1991; Young an explosion in our knowledge of brain connectivity (e.g. Zeki & Shipp 1988; Felleman & Van Essen 1991; Young 1993; Scannell *et al.* 1995; Pandya & Yeterian 1985), but have contributed very little to our knowledge of the Zeki & Shipp 1988; Felleman & Van Essen 1991; Young 1993; Scannell *et al.* 1995; Pandya & Yeterian 1985), but have contributed very little to our knowledge of the magnitude of and variability in individual brain 1993; Scannell *et al.* 1995; Pandya & Yeterian 1985), but
have contributed very little to our knowledge of the
magnitude of, and variability in, individual brain
connections. This is because quantification remains have contributed very little to our knowledge of the magnitude of, and variability in, individual brain connections. This is because quantification remains magnitude of, and variability in, individual brain
connections. This is because quantification remains
particularly laborious (but see Olson & Musil 1992;
Musil & Olson 1988a b 1991; MacNeil et al. 1997; connections. This is because quantification remains
particularly laborious (but see Olson & Musil 1992;
Musil & Olson 1988*a*,*b*, 1991; MacNeil *et al.* 1997;
Hilgetag & Grant, this issue). Therefore, the yast particularly laborious (but see Olson & Musil 1992;
Musil & Olson 1988a,b, 1991; MacNeil et al. 1997;
Hilgetag & Grant, this issue). Therefore, the vast
majority of corticocortical and thalamocortical connec-Musil & Olson 1988a,b, 1991; MacNeil et al. 1997; Hilgetag & Grant, this issue). Therefore, the vast majority of corticocortical and thalamocortical connection tracing studies still use a small number of individuals and report qualitative, rather than quantitative, majority of corticocortical and thalamocortical connection tracing studies still use a small number of individuals and report qualitative, rather than quantitative, measures of connection density. tion tracing studies still use a small number of indivi-

Recently, MacNeil *et al*. (1997) published quantitative data on the strengths of cortical and thalamic projections *PHO*, TOIYAK 1927, 1999). These advances have resulted in the data on the strengths of cortical and that that projections *hil. Trans. R. Soc. Lond.* B (2000) **355**, 21–35 21 © 2000 The Royal Society

BIOLOGICAL
SCIENCES ROYAI THE

PHILOSOPHICAL
TRANSACTIONS

BIOLOGICAL CIENCES

ROYA

THE

PHILOSOPHICAL
TRANSACTIONS

to the middle suprasylvian (MS) visual cortical area in
the cat. This study used several different tracers, but was the middle suprasylvian (MS) visual cortical area in
the cat. This study used several different tracers, but was
erv careful to minimize variability in the areal extent of b the middle suprasylvian (MS) visual cortical area in
he cat. This study used several different tracers, but was
ery careful to minimize variability in the areal extent of
he tracer denosit. MacNeil *et al.* (1997) inclu he cat. This study used several different tracers, but was
ery careful to minimize variability in the areal extent of
he tracer deposit. MacNeil *et al.* (1997) included only
asses where the tracer was confined to a partic ery careful to minimize variability in the areal extent of
he tracer deposit. MacNeil *et al.* (1997) included only
ases where the tracer was confined to a particular retihe tracer deposit. MacNeil *et al.* (1997) included only ases where the tracer was confined to a particular retion of MS cortex, where the tracer reached all ortical layers (but not the white matter) where the ases where the tracer was confined to a particular reti-
otopic region of MS cortex, where the tracer reached all
ortical layers (but not the white matter), where the
caser denosit was a reasonable size and where the white otopic region of MS cortex, where the tracer reached all
ortical layers (but not the white matter), where the
racer deposit was a reasonable size and where the white
atter was not damaged by the injection Their data ortical layers (but not the white matter), where the racer deposit was a reasonable size and where the white
atter was not damaged by the injection. Their data
aw a low level of variability in the strength of indiviracer deposit was a reasonable size and where the white

atter was not damaged by the injection. Their data

at a low a low level of variability in the strength of indivi-

and the strength of indivi-

and the strength of atter was not damaged by the injection. Their data
have a low level of variability in the strength of indivi-
ual thalamocortical connections, but a very high degree
f variability in the strength of individual corticocorti Now a low level of variability in the strength of individual thalamocortical connections, but a very high degree f variability in the strength of individual corticocortical \blacktriangleright onnections. variability in the strength of individual corticocortical
nnections.
The work of MacNeil *et al.* (1997) inspired us to pool
antitative connection data from our laboratories with

• onnections.
• The work of MacNeil *et al.* (1997) inspired us to pool
• uantitative connection data from our laboratories with
• ublished studies to investigate variability more system-Figure 1 The work of MacNeil *et al.* (1997) inspired us to pool
quantitative connection data from our laboratories with
ublished studies to investigate variability more system-
disculy This effort is important because va I uantitative connection data from our laboratories with

ublished studies to investigate variability more system-

itically. This effort is important because variability has

the degree and ublished studies to investigate variability more system-
itically. This effort is important because variability has
at least four serious implications. First, the degree and
ature of variability have practical consequences This effort is important because variability has

It least four serious implications. First, the degree and
 Ω ature of variability have practical consequences for
 Ω serimental design in neuroanatomical studies and It least four serious implications. First, the degree and Ω ature of variability have practical consequences for sperimental design in neuroanatomical studies and for he way that results are reported. Most single studi Follow are practical consequences for
experimental design in neuroanatomical studies and for
he way that results are reported. Most single studies
se small samples from which it is impossible to make a xperimental design in neuroanatomical studies and for
he way that results are reported. Most single studies
se small samples from which it is impossible to make a
easonable estimate of the distribution from which the he way that results are reported. Most single studies
se small samples from which it is impossible to make a
easonable estimate of the distribution from which the
sample came. However, any form of statistical inference se small samples from which it is impossible to make a
easonable estimate of the distribution from which the
ample came. However, any form of statistical inference,
ven one as simple as calculating the standard exercise estimate of the distribution from which the sample came. However, any form of statistical inference, ven one as simple as calculating the standard eviation has to make assumptions about the likely ample came. However, any form of statistical inference,
ven one as simple as calculating the standard
eviation, has to make assumptions about the likely
istribution of the data. By pooling data from a number ven one as simple as calculating the standard eviation, has to make assumptions about the likely istribution of the data. By pooling data from a number eviation, has to make assumptions about the likely
istribution of the data. By pooling data from a number
f studies we can obtain a reasonable picture of this
istribution, that can then be 'assumed' by other istribution of the data. By pooling data from a number
f studies we can obtain a reasonable picture of this
istribution, that can then be 'assumed' by other
searchers. If our pooled data show that variability is f studies we can obtain a reasonable picture of this istribution, that can then be 'assumed' by other esearchers. If our pooled data show that variability is in the sample size and random sampling error istribution, that can then be 'assumed' by other esearchers. If our pooled data show that variability is igh, then sample size and random sampling error ecome important issues esearchers. If our pooled
igh, then sample size a
ecome important issues.
Second variability can

gh, then sample size and random sampling error
come important issues.
Second, variability can also have implications for the
w that results are reported by anatomists and iterpreted by other researchers. For example, given very vay that results are reported by anatomists and
terpreted by other researchers. For example, given very
ariable connection densities, no single tracer injection is
kely to produce a very 'typical' pattern of labelling in iterpreted by other researchers. For example, given very
ariable connection densities, no single tracer injection is
kely to produce a very 'typical' pattern of labelling in
he rest of the cortex and all individual results ariable connection densities, no single tracer injection is
kely to produce a very 'typical' pattern of labelling in
he rest of the cortex and all individual results are likely
a depart, substantially, from the average or kely to produce a very 'typical' pattern of labelling in
he rest of the cortex and all individual results are likely
b depart substantially from the average or most
epresentative case. This presents challenges for those represent of the cortex and all individual results are likely
of depart substantially from the average or most
epresentative case. This presents challenges for those
sing connection information for data analytic studies b depart substantially from the average or most
epresentative case. This presents challenges for those
sing connection information for data analytic studies
 λ a Noung 1993: Scannell 1997: Stephan Zilles & Kötter epresentative case. This presents challenges for those
sing connection information for data analytic studies
e.g. Young 1993; Scannell 1997; Stephan, Zilles & Kötter,
his issue) or synthetic modelling studies (e.g. Kötter the sing connection information for data analytic studies

at angle sequence of the single studies (e.g. Kötter & m

dis issue) or synthetic modelling studies (e.g. Kötter & m

transference this issue) e.g. Young 1993; Scar
his issue) or synthet
ommer, this issue).
Third individual his issue) or synthetic modelling studies (e.g. Kötter & ommer, this issue).
Third, individual differences in connection densities

have great functional importance. For example, they have a causal role in shaping individual differences and have great functional importance. For example, they as have a causal role in shaping individual differences
and behaviour. However, to our knowledge, no attempt has et been made to untangle the contributions of between ay have a causal role in shaping individual differences
at behaviour. However, to our knowledge, no attempt has
et been made to untangle the contributions of between-
adividual variability from within-individual variabilit in behaviour. However, to our knowledge, no attempt has

et been made to untangle the contributions of between-

dividual variability from within-individual variability.

Striptility in the results of connection tracing ex \Box et been made to untangle the contributions of between-
 \bigcup dividual variability from within-individual variability.
 \bigcap ariability in the results of connection tracing experi-Individual variability from within-individual variability.

Integrative in the results of connection tracing experi-

lents in different animals will have several sources.

Sources include within-animal factors, which woul For an ability in the results of connection tracing experients in different animals will have several sources ources include within-animal factors, which would be research even if the same experiment could be repeated prents in different animals will have several sources.
ources include within-animal factors, which would be resent even if the same experiment could be repeated
in the same animal (e.g. experimental error within-area ources include within-animal factors, which would be
resent even if the same experiment could be repeated
in the same animal (e.g. experimental error, within-area
eterogeneity in projection patterns) and factors that resent even if the same experiment could be repeated
in the same animal (e.g. experimental error, within-area
eterogeneity in projection patterns), and factors that
effect systematic differences between animals (e.g. inte n the same animal (e.g. experimental error, within-area
eterogeneity in projection patterns), and factors that
effect systematic differences between animals (e.g. inter-
 $\sum_{n=1}^{\infty}$ interanimal di¡erences in connectivity). In the study of effect systematic differences between animals (e.g. inter-
 $\frac{1}{2}$ nimal differences in connectivity). In the study of $\frac{1}{2}$ acness that $\frac{1}{2}$ a single tracer substance was enosited at a single location within e Ω nimal differences in connectivity). In the study of $4ac$ Neil *et al.* (1997), a single tracer substance was eposited at a single location within each single animal. AacNeil *et al.* (1997), a single tracer substance was eposited at a single location within each single animal.
Jowever, repeated measures within a subject are eposited at a single location within-each single animal.
Iowever, repeated measures within-a subject are
ecessary to estimate within-individual variability.
Jeally, such measures should be made with tracers that ecessary to estimate within-individual variability.

possess virtually identical uptake, transport and visibility
characteristics. While. MacNeil, et al., made, efforts, the possess virtually identical uptake, transport and visibility
characteristics. While MacNeil *et al.* made efforts the
minimize variability in the spatial extent of tracer possess virtually identical uptake, transport and visibility
characteristics. While MacNeil *et al.* made efforts the
minimize variability in the spatial extent of tracer
denosits (e.g. by making large denosits to avoid l characteristics. While MacNeil *et al.* made efforts the minimize variability in the spatial extent of tracer deposits (e.g. by making large deposits to avoid labelling only certain subcompartments of MS) in the absence minimize variability in the spatial extent of tracer
deposits (e.g. by making large deposits to avoid labelling
only certain subcompartments of MS), in the absence of
reneated measures their results cannot distinguish deposits (e.g. by making large deposits to avoid labelling
only certain subcompartments of MS), in the absence of only certain subcompartments of MS), in the absence of
repeated measures, their results cannot distinguish
between-individual variability from within-individual
variability. Therefore, the magnitude of betweenrepeated measures, their results cannot distinguish
between-individual variability from within-individual
variability. Therefore the magnitude of between-
individual differences is unclear between-individual variability from within-individual
variability. Therefore the magnitude of between-
individual differences is unclear. riability. Therefore the magnitude of between-
dividual differences is unclear.
To help resolve this situation, for the rest of this paper
and rest of this paper

individual differences is unclear.
To help resolve this situation, for the rest of this paper
we make a strict distinction between within-individual
and inter-individual cases 'Within-individual' refers to the To help resolve this situation, for the rest of this paper
we make a strict distinction between within-individual
and inter-individual cases. Within-individual' refers to the
results that would be obtained if repeated inje we make a strict distinction between within-individual
and inter-individual cases. Within-individual' refers to the
results that would be obtained if repeated injections were and inter-individual cases. Within-individual' refers to the results that would be obtained if repeated injections were made in the same cortical area of the same individual. Within-individual variability will be due to ra results that would be obtained if repeated injections were
made in the same cortical area of the same individual.
Within-individual variability will be due to random
experimental error and to local differences in connecmade in the same cortical area of the same individual.
Within-individual variability will be due to random
experimental error and to local differences in connec-
tivity or tracer untake within a cortical area 'Inter-indivi Within-individual variability will be due to random
experimental error and to local differences in connec-
tivity or tracer uptake within a cortical area.'Inter-indivi-
dual' refers to the results that would be obtained if experimental error and to local differences in connectivity or tracer uptake within a cortical area. Inter-individual' refers to the results that would be obtained if single injections were made in the same cortical area o tivity or tracer uptake within a cortical area. Inter-individual' refers to the results that would be obtained if single
injections were made in the same cortical area of different
individuals. Inter-individual variability dual' refers to the results that would be obtained if single
injections were made in the same cortical area of different injections were made in the same cortical area of different
individuals. Inter-individual variability will be due to
systematic differences between individuals plus within-
individual variability. The difference between in individuals. Inter-individual variability will be due to
systematic differences between individuals plus within-
individual variability. The difference between inter- and
within-individual variability should let us estimat systematic differences between individuals plus within-
individual variability. The difference between inter- and
within-individual variability should let us estimate the individual variability. The difference between inter- and
within-individual variability should let us estimate the
proportion of variance that is due to within-animal
factors and the proportion of variance that is due to within-individual variability should let us estimate the proportion of variance that is due to within-animal factors and the proportion of variance that is due to between-animal factors proportion of variance
factors and the proporti
between-animal factors.
Eourth the distribution factors and the proportion of variance that is due to
between-animal factors.
Fourth, the distribution of connection densities may

ecome important issues.

Second, variability can also have implications for the (ii)each neuron has a small and fixed probability of

vay that results are reported by anatomists and projecting to area B; (iii) neurons in a between-animal factors.
Fourth, the distribution of connection densities may
provide important insights into the organization of cortico-
cortical and thalamocortical connections We illustrate this Fourth, the distribution of connection densities may
provide important insights into the organization of cortico-
cortical and thalamocortical connections. We illustrate this
point with a simplistic, and almost certainly i provide important insights into the organization of cortico-
cortical and thalamocortical connections. We illustrate this
point with a simplistic, and almost certainly incorrect,
model. The model makes the following assump cortical and thalamocortical connections. We illustrate this
point with a simplistic, and almost certainly incorrect,
model. The model makes the following assumptions: point with a simplistic, and almost certainly incorrect,
model. The model makes the following assumptions:
(i) there are a very large number of neurons in area A;
(ii)each neuron has a small and fixed probability of model. The model makes the following assumptions:
(i) there are a very large number of neurons in area A;
(ii)each neuron has a small and fixed probability of
projecting to area B: (iii) neurons in area A project to area (i) there are a very large number of neurons in area A;
(ii) each neuron has a small and fixed probability of
projecting to area B; (iii) neurons in area A project to area
B, independently of each other: (iv) the probabil B independently of each other; (iv) the probability of a projecting to area B; (iii) neurons in area A project to area
B independently of each other; (iv) the probability of a
neuron projecting from A to B is equal across all of area A
and area B: (v) we make identical tracer i B independently of each other; (iv) the probability of a
neuron projecting from A to B is equal across all of area A
and area B; (v) we make identical tracer injections in
different individuals neuron projecting from

and area B; (v) we indifferent individuals.

The model that we and area B; (v) we make identical tracer injections in different individuals.
The model that we have just outlined describes a

different individuals.
The model that we have just outlined describes a
Poisson process. If it were true, we would expect the
distribution of connection densities for any particular The model that we have just outlined describes a
Poisson process. If it were true, we would expect the
distribution of connection densities for any particular
connection to be given by equation (1). Here μ is the Poisson process. If it were true, we would expect the distribution of connection densities for any particular connection to be given by equation (1). Here, μ is the mean number of labelled neurons in area A following a distribution of connection densities for any particular
connection to be given by equation (1). Here, μ is the
mean number of labelled neurons in area A following a
tracer injection in area B and $h(r)$ is the probabili connection to be given by equation (1). Here, μ is the mean number of labelled neurons in area A following a tracer injection in area B, and $p(r)$ is the probability of finding the number r of labelled neurons in area mean number of labelled neurons in area A following a tracer injection in area B, and $p(r)$ is the probability of finding the number, r , of labelled neurons in area A.

$$
p(r) = \frac{\mu^r e^{-\mu}}{r!}.
$$
 (1)

For all but the weakest connections, the model predicts For all but the weakest connections, the model predicts normally distributed connection densities, where the stan-
dard deviation is equal to the square root of μ . Deviations For all but the weakest connections, the model predicts
normally distributed connection densities, where the stan-
dard deviation is equal to the square root of μ . Deviations
from the model would show that other proces normally distributed connection densities, where the standard deviation is equal to the square root of μ . Deviations from the model would show that other processes contri-
bute to variability in connections. Different dard deviation is equal to the square root of μ . Deviations
from the model would show that other processes contri-
bute to variability in connections. Different models of
cortical organization predict different kinds o from the model would show that other processes contribute to variability in connections. Different models of cortical organization predict different kinds of variability.
For example, birbly variable distributions are comm bute to variability in connections. Different models of cortical organization predict different kinds of variability.
For example, highly variable distributions are common in highlow where local processes are Poisson, but cortical organization predict different kinds of variability.
For example, highly variable distributions are common in
biology where local processes are Poisson, but where the mean of the process varies from site to site or from indivibiology where local processes are Poisson, but where the
mean of the process varies from site to site or from indivi-
dual to individual (e.g. Solomon 1983; Shaw *et al.* 1998;
Stear *et al.* 1998). So, given patchy connec mean of the process varies from site to site or from individual to individual (e.g. Solomon 1983; Shaw *et al.* 1998; Stear *et al.* 1998). So, given patchy connections between cortical areas we would expect a bighly varia dual to individual (e.g. Solomon 1983; Shaw *et al.* 1998; Stear *et al.* 1998). So, given patchy connections between cortical areas, we would expect a highly variable distribution of connection densities (Montero 1981: R Stear *et al.* 1998). So, given patchy connections between cortical areas, we would expect a highly variable distribution of connection densities (Montero 1981; Raczkowski & Rosenquist 1983; Symonds & Rosenquist 1984; De V cortical areas, we would expect a highly variable distribution of connection densities (Montero 1981; Raczkowski
& Rosenquist 1983; Symonds & Rosenquist 1984; De Yoe

& Van Essen 1985; Sherk 1986; Zeki & Shipp 1988, 1989; $\frac{1}{2}$ Van Essen 1985; She
hipp & Grant 1991).

2. METHODS

(a) *Quantitative connection data*

(a) *Quantitative connection data*
We used quantitative data from published retrograde tracing
disc (Olson & Musil 1002; Musil & Olson 1099*c* & 1001) and (a) *Quantitative connection data*
We used quantitative data from published retrograde tracing
idies (Olson & Musil 1992; Musil & Olson 1988*a*,*b*, 1991) and
im our own laboratories. The published studies wed the fluores udies (Olson & Musil 1992; Musil & Olson 1988 a, b , 1991) and
om our own laboratories. The published studies used the fluorescudies (Olson & Musil 1992; Musil & Olson 1988a,b, 1991) and

om our own laboratories. The published studies used the fluores-

ent retrograde tracers nuclear yellow (NY) and bisbenzimide
 B_1) to investigate the connec (com our own laboratories. The published studies used the fluores-
 \pm intertograde tracers nuclear yellow (NY) and bisbenzimide
 \pm Bb) to investigate the connections of medial prefrontal cortex
 \pm BECm) area from (Bb) to investigate the connections of medial prefrontal cortex
(PFCm), area 6m, and anterior and posterior cingulate areas \blacktriangleright CGa and CGp) of the cat. These studies are particularly useful PFCm), area 6m, and anterior and posterior cingulate areas
CGa and CGp) of the cat. These studies are particularly useful
cause two tracers were frequently placed in the same cortical
large of the same individual. Each the CGa and CGp) of the cat. These studies are particularly useful
ecause two tracers were frequently placed in the same cortical
rea of the same individual. For the rest of this paper, we assume
and NV and Bb have very simil \Box rea of the same individual. For the rest of this paper, we assume at NY and Bb have very similar neuronal uptake and transport Frea of the same individual. For the rest of this paper, we assume

at NY and Bb have very similar neuronal uptake and transport

haracteristics, so that they sample the same sets of connections. The NY and Bb have very similar neuronal uptake and transport

haracteristics, so that they sample the same sets of connections.

This assumption lets us use these double-label studies to estimate

distributed variability \sum his assumption lets us use these double-label studies to estimate \sum ithin-individual variability in connection patterns. is assumption lets us use these double-label studies to estimate
thin-individual variability in connection patterns.
The data from our laboratories were obtained from injec-
ps. of the retrograde tracers WCA HPP. Fluoresco

The data from our laboratories were obtained from injec-
ons of the retrograde tracers WGA-HRP, Fluorogold or
adamine labelled later mineapheres (MGA-HRP, $\frac{1007}{1007}$ ons of the retrograde tracers WGA-HRP, Fluorogold or nodamine-labelled latex microspheres (MacNeil *et al.* 1997; Grant & Shipp 1991). The tracers were injected into either the nodamine-labelled latex microspheres (MacNeil *et al.* 1997; cannot & Shipp 1991). The tracers were injected into either the reduced in the space of the space (MacNeil *et al.* 1997; Grant & said him 1001) on the next encl Frant & Shipp 1991). The tracers were injected into either the
siddle suprasylvian visual area (MacNeil *et al.* 1997; Grant &
hipp 1991) or the posterolateral lateral suprasylvian visual
res (PUS: Crant & Shipp 1991) Det hipp 1991) or the posterolateral lateral suprasylvian visual rea (PLLS; Grant & Shipp 1991). Details of our methods are published elsewhere (MacNeil *et al.* 1997; Grant & Shipp 1991). rea (PLLS; Grant & Shipp 1991). Details of our methods are
ublished elsewhere (MacNeil *et al.* 1997; Grant & Shipp 1991).
 $\frac{1}{2}$ minimize variability due to spatial variation in the tracer
 $\frac{1}{2}$ massive (Crant & ublished elsewhere (MacNeil *et al.* 1997; Grant & Shipp 1991).
 α minimize variability due to spatial variation in the tracer

eposits (Grant & Shipp 1991; MacNeil *et al.* 1997), we

example aggregate if they not all eposits (Grant & Shipp 1991; MacNeil *et al.* 1997), we ccepted cases only if they met all the following criteria. First, tacer deposits exposed a reasonable area of the cortex to the ccepted cases only if they met all the following criteria. First,
care deposits exposed a reasonable area of the cortex to the
care substance, with the aim of avoiding differential labelling
a subset of offenent naunane wi Facer deposits exposed a reasonable area of the cortex to the care substance, with the aim of avoiding differential labelling is subsets of afferent neurons with small or patchy terminal subspirations (Shork & Ombasllone a subsets of afferent neurons with small or patchy terminal rborizations (Sherk & Ombrellaro 1988; Payne *et al.* 1991; 1 subsets of afferent neurons with small or patchy terminal
rborizations (Sherk & Ombrellaro 1988; Payne *et al.* 1991;
hipp & Grant 1991). Second, all cortical layers were exposed
at trees so suce differential labelling rborizations (Sherk & Ombrellaro 1988; Payne *et al.* 1991;
hipp & Grant 1991). Second, all cortical layers were exposed
of tracer, so avoiding differential labelling in subsets of afferent
awons with different laminar te I tracer, so avoiding differential labelling in subsets of afferent eurons with different laminar terminations. Third, tracer had ot spread into the white matter. And fourth, the label had not eurons with different laminar terminations. Third, tracer had eurons with different laminar terminations. Third, tracer had
ot spread into the white matter. And fourth, the label had not
oread into the adjacent sulcus or lateral suprasylvian areas.
on the data from the labenature of ot spread into the white matter. And fourth, the label had not
oread into the adjacent sulcus or lateral suprasylvian areas.
or the data from the laboratory of Dr Payne, tracer deposits
or a set limited to a particular par or the data from the laboratory of Dr Payne, tracer deposits ere also limited to a particular region of the visual field representation.

Retrogradely labelled neurons in cortical areas or thalamic Presentation.

Retrogradely labelled neurons in cortical areas or thalamic

uclei distant to the injection sites were counted. The propor-
 $\sum_{n=1}^{\infty}$ of labelled thelamic or contical neurons in our given Retrogradely labelled neurons in cortical areas or thalamic
uclei distant to the injection sites were counted. The propor-
on, S_i , of labelled thalamic or cortical neurons in any given
nea you then coloulated by dividin on, S_i , of labelled thalamic or cortical neurons in any given rea was then calculated by dividing the number of neurons in on, S_i , of labelled thalamic or cortical neurons in any given
rea was then calculated by dividing the number of neurons in
a rea or nucleus, R_i , by the total number of counted neurons,
in the series or thalamus repres **The correct value of neural correct or thalamus, respectively (equation (2)).

The cortex or thalamus, respectively (equation (2)).**

$$
\sum_{i} = \frac{R_i}{T} \tag{2}
$$

 $\mathcal{D}_i = \frac{1}{T}$ (2)

This strategy eliminates any potential differences in the efficacy
 \mathcal{D}_i is strategy eliminates any potential differences in the efficacy This strategy eliminates any potential differences in the efficacy

of labelling of cortical and thalamic neurons that might exist.

cosible contributing variables include differences in numbers f labelling of cortical and thalamic neurons that might exist.
ossible contributing variables include differences in numbers, f labelling of cortical and thalamic neurons that might exist.

ossible contributing variables include differences in numbers,

zes and concentrations of terminals along cortical and

zelonia augusta arbours and difference ossible contributing variables include differences in numbers,
zes and concentrations of terminals along cortical and
nalamic axon arbours, and differences in neuronal transport
negligies. Menseum supposeins of lobelling d ralamic axon arbours, and differences in neuronal transport apacities. Moreover, expression of labelling densities in the ralamic axon arbours, and differences in neuronal transport
apacities. Moreover, expression of labelling densities in the
 $\sum_{n=1}^{\infty}$ of proportions removes the variability in connection
matrix that result from absolut \sum_{sum} apacities. Moreover, expression of labelling densities in the \sum_{sum} of proportions removes the variability in connection ensities that result from absolute differences in tracer uptake ensities that result from absolute differences in tracer uptake
etween injections and emphasizes differences in the pattern of ensities that result from absolute differences in tracer uptake
etween injections and emphasizes differences in the pattern of
belling. When we refer to connection strength or density
bewhen in this paper, it is these perm etween injections and emphasizes differences in the pattern of
belling. When we refer to connection strength or density
lsewhere in this paper, it is these normalized values to which we
for Hauman pakers noticially we have lsewhere in this paper, it is these normalized values to which we
efer. However, where possible we have repeated the analyses

with the raw, unnormalized, cell counts from our own laborawith the raw, unnormalized, cell counts from
tories. The raw data yield very similar results.
Scaling, presentes, relative mean, connection tories. The raw data yield very similar results.
Scaling preserves relative mean connection density across

tories. The raw data yield very similar results.
Scaling preserves relative mean connection density across
comparable injections, but causes systematic underestimation of
the variability of connections. This is because the Scaling preserves relative mean connection density across
comparable injections, but causes systematic underestimation of
the variability of connections. This is because the total number
of labelled calle T covaries wit comparable injections, but causes systematic underestimation of
the variability of connections. This is because the total number
of labelled cells, *T*, covaries with the number of labelled cells in
seek area an nucleus the variability of connections. This is be
of labelled cells, *T*, covaries with the nur
each area or nucleus, R_i (equation (2)). each area or nucleus, R_i (equation (2)).

$$
T = R_1 + R_2 + R_3 + \dots
$$
 (3)

The variance of the scaled total (T/T) is, by definition, zero. The variance of the scaled total (T/T) is, by definition, zero.
The covariation between *T* and R_i is negligible for weak
connections but substantial for strong connections. For example The variance of the scaled total (T/T) is, by definition, zero.
The covariation between T and R_i is negligible for weak
connections but substantial for strong connections. For example,
given recognable examptions about connections but substantial for strong connections. For example, given reasonable assumptions about the nature of the covariance, standard deviations calculated from scaled data on given reasonable assumptions about the nature of the covariance, standard deviations calculated from scaled data on
connections containing 50%, 25% and 10% of labelled neurons
will be 0.5.0.7 and 0.95 of their two volume F iance, standard deviations calculated from scaled data on
connections containing 50%, 25% and 10% of labelled neurons
will be 0.5, 0.7 and 0.85 of their true values. Fortunately, it is
possible to estimate and correct for connections containing 50%, 25% and 10% of labelled neurons
will be 0.5, 0.7 and 0.85 of their true values. Fortunately, it is
possible to estimate and correct for this scaling bias (see $\S 3(e)$). **(b)** *Inter- and intra-individual samples*

(b) *Inter- and intra-individual samples*
For each corticocortical or thalamocortical connection, we
laulated the mass and standard deviation of the presention of (b) *Inter- and intra-individual samples*
For each corticocortical or thalamocortical connection, we
calculated the mean and standard deviation of the proportion of
proportional leaded newspape following traces injections calculated the mean and standard deviation of the proportion of
retrogradely labelled neurons following tracer injections. These calculated the mean and standard deviation of the proportion of
retrogradely labelled neurons following tracer injections. These
sample statistics were computed from data for the same connec-
tion repeatedly measured withi retrogradely labelled neurons following tracer injections. These
sample statistics were computed from data for the same connec-
tion repeatedly measured within single published studies or
single laberatories We did not mak tion repeatedly measured within single published studies or
single laboratories.We did not make any composite samples using tion repeatedly measured within single published studies or
single laboratories. We did not make any composite samples using
data from different laboratories even when the same connections
wave measured. This is because ou single laboratories. We did not make any composite samples using
data from different laboratories even when the same connections
were measured. This is because any differences in the proportion
of earter searched for label were measured. This is because any differences in the proportion
of cortex searched for labelled neurons or differences in counting
methods could introduce errors into our calculations. of cortex searched for labelled neurons or differences in counting

To separate the within-individual from the inter-individual methods could introduce errors into our calculations.
To separate the within-individual from the inter-individual
cases, we divided the results of studies where more than one
trease was injected into an animal inte two hin To separate the within-individual from the inter-individual
cases, we divided the results of studies where more than one
tracer was injected into an animal, into two kinds of subsamples
(toble 1). The first inter individua cases, we divided the results of studies where more than one
tracer was injected into an animal, into two kinds of subsamples
(table 1*a*). The first inter-individual subsamples (table 1*a*) were
arranged as that thay did tracer was injected into an animal, into two kinds of subsamples

(table 1). The first inter-individual subsamples (table 1*a*) were

arranged so that they did not contain more than one measure

from any single animal. The arranged so that they did not contain more than one measure from any single animal. The variability of these samples provides
an estimate of inter-individual variability. The within-individual
subsamples (table $1b$) consisted of paired injections in the same an estimate of inter-individual variability. The within-individual an estimate of inter-individual variability. The within-individual
subsamples (table 1b) consisted of paired injections in the same
area of the same hemisphere of the same animal. These samples
provide an estimate of with subsamples (table $1b$) consisted of paired injections area of the same hemisphere of the same animal. The provide an estimate of within-individual variability. provide an estimate of within-individual variability.
3. RESULTS

By pooling data from our laboratories and from the literature, we were able to obtain quantitative connection data on the relative densities of 130 corticocortical and 54 literature, we were able to obtain quantitative connection
data on the relative densities of 130 corticocortical and 54
thalamocortical connections. Quantitative connectional
neuroanatomy is extremely laborious so sample s data on the relative densities of 130 corticocortical and 54
thalamocortical connections. Quantitative connectional
neuroanatomy is extremely laborious, so sample sizes for
each connection were small. There were typically thalamocortical connections. Quantitative connectional
neuroanatomy is extremely laborious, so sample sizes for
each connection were small. There were typically three to
five tracer injections per connection, with a range neuroanatomy is extremely laborious, so sample sizes for
each connection were small. There were typically three to
five tracer injections per connection, with a range of two to ten. For the data from our laboratories we found five tracer injections per connection, with a range of two
to ten. For the data from our laboratories we found
between 1000 and 25 000 retrogradely labelled neurons
in the thalamus or cortex per tracer injection. Because o to ten. For the data from our laboratories we found
between 1000 and 25 000 retrogradely labelled neurons
in the thalamus or cortex per tracer injection. Because of
the small number of injections per connection no single between 1000 and 25 000 retrogradely labelled neurons
in the thalamus or cortex per tracer injection. Because of
the small number of injections per connection, no single
connection provides enough data for a good estimate in the thalamus or cortex per tracer injection. Because of the small number of injections per connection, no single connection provides enough data for a good estimate of the distribution of densities. the small number of injections per connection, no single

(a) *Great variability in individual connection densities*

The high degree of variability in the densities of indivi**densities**
The high degree of variability in the densities of individual corticocortical and thalamocortical connections is
illustrated in figure 1. Figure 14, shows cases where the The high degree of variability in the densities of individual corticocortical and thalamocortical connections is
illustrated in figure 1. Figure 1*a* shows cases where the
density of the same thalamocortical connection var dual corticocortical and thalamocortical connections is illustrated in figure 1. Figure 1a shows cases where the density of the same thalamocortical connection varies

BIOLOGICAL SCIENCES

INXO

ш HL

PHILOSOPHICAL
TRANSACTIONS

Table 1. *Distinguishing between within-individual and inter-*
 dividual variability individual variability

(The table shows how we treat data from studies that made two
the table shows how we treat data from studies that made two
care injections within single individuals. Here, two animals tracer injections with the tracer injections within single individuals. Here, two animals
that made two sacer injections within single individuals. Here, two animals
at 69 and cat 89) each received two tracer injections (B The table shows how we treat data from studies that made two
care injections within single individuals. Here, two animals
cat 69 and cat 89) each received two tracer injections (Bb and
(Y) and the proportions of labelled n **SCIENCES** Facer injections within single individuals. Here, two animals cat 69 and cat 89) each received two tracer injections (Bb and IY) and the proportions of labelled neurons in thalamic nuclei (Fer recorded (a) To estimate th 2xt 69 and cat 89) each received two tracer injections (Bb and $[Y]$) and the proportions of labelled neurons in thalamic nuclei vere recorded. (*a*) To estimate the inter-individual variability a connection density (conta IY) and the proportions of labelled neurons in thalamic nuclei

'ere recorded. (a) To estimate the inter-individual variability
 $\frac{1}{1}$ connection density (containing within- plus between-animal
 $\frac{1}{1}$ ctors), we d factor exceeding the inter-individual variability
of a connection density (containing within- plus between-animal
actors), we did not average across all four injections. Rather, 1 connection density (containing within- plus between-animal
tors), we did not average across all four injections. Rather,
 e produced two subsamples in which neither animal was
presented more than once. Means and standa represented more versions all four injections. Rather,

The produced two subsamples in which neither animal was

presented more than once. Means and standard deviations

ere then computed for the subsamples. In practice, s e produced two subsamples in which neither animal was
presented more than once. Means and standard deviations
rere then computed for the subsamples. In practice, such
ubsamples contained data from two to seven animals. (b spresented more than once. Means and standard deviations ere then computed for the subsamples. In practice, such absamples contained data from two to seven animals. (b) To stimate the intra-variability in connection density (containing
all ply within-animal factors), we did not average across all four
apjections. Rather, we produced subsamples, each of which
pontained data from only one anim stimate the intra-variability in connection density (containing I have within-animal factors), we did not average across all four
apjections. Rather, we produced subsamples, each of which
pontained data from only one animal. Means and standard
eviations were then computed for the subsa \blacktriangleright nly within-animal factors), we did not average across all four piections. Rather, we produced subsamples, each of which deviations. Rather, we produced subsamples, each of which
pottained data from only one animal. Means and standard
eviations were then computed for the subsamples. The size of
see subsamples was always two. because no more pontained data from only one animal. Means and standard
eviations were then computed for the subsamples. The size of
rese subsamples was always two, because no more than two
istinguishable tracers (NY and Bb) were ever inj eviations were then computed for the subsamples. The size of
rese subsamples was always two, because no more than two
istinguishable tracers (NY and Bb) were ever injected into the
ame individual.) istinguishable tracers (NY and Bb) were ever injected into the

BIOLOGICAL

Figure 1. Typical examples of variability in extrinsic Figure 1. Typical examples of variability in extrinsic
thalamocortical (a) , and corticocortical (b) , connection
density. The vertical axis shows the log of the proportion of Figure 1. Typical examples of variability in extrinsic
thalamocortical (a) , and corticocortical (b) , connection
density. The vertical axis shows the log of the proportion of
labelled neurons in an afferent area or nucle thalamocortical (a) , and corticocortical (b) , connection
density. The vertical axis shows the log of the proportion of
labelled neurons in an afferent area or nucleus following a
retrograde tracer injection. Each point density. The vertical axis shows the log of the proportion
labelled neurons in an afferent area or nucleus following
retrograde tracer injection. Each point represents the
proportion of total labelled cortical or thalamic labelled neurons in an afferent area or nucleus following a
retrograde tracer injection. Each point represents the
proportion of total labelled cortical or thalamic neurons
following a single retrograde tracer injection in retrograde tracer injection. Each point represents the
proportion of total labelled cortical or thalamic neurons
following a single retrograde tracer injection in a single individual. The mean density of the strong connections (e.g. CGp to CGa) may be over 1000 times that of the weak individual. The mean density of the strong connections (e.g. CGp to $CGa)$ may be over 1000 times that of the weak
connections (e.g. PS to PMLS). There is also great variability
in the proportion of labelled neurons for t CGp to $CGa)$ may be over 1000 times that of the weak
connections (e.g. PS to $PMLS$). There is also great variability
in the proportion of labelled neurons for the same connection
across different tracer injections. For e connections (e.g. PS to PMLS). There is also great variability
in the proportion of labelled neurons for the same connection
across different tracer injections. For example, the proportion
of labelled cortical neurons in c in the proportion of labelled neurons for the same connection
across different tracer injections. For example, the proportion
of labelled cortical neurons in cortical area PS following across different tracer injections. For example, the proportion
of labelled cortical neurons in cortical area PS following
injections in PMLS, and the proportion of labelled neurons in
cortical area CGa following injection of labelled cortical neurons in cortical area PS following
injections in PMLS, and the proportion of labelled neurons in
cortical area CGa following injections in PFCm, vary over
100-fold (a). Similarly, the proportion of injections in PMLS, and the proportion of labelled neurons in
cortical area CGa following injections in PFCm, vary over
100-fold (*a*). Similarly, the proportion of labelled thalamic
neurons in RH and MD following injectio cortical area CGa following injections in PFCm, vary over 100-fold (*a*). Similarly, the proportion of labelled thalamic neurons in RH and MD following injections in CGa varies over tenfold (*b*) 100-fold (a) . Simil
neurons in RH an
over tenfold (b) .

over tenfold (b) .
over a factor of ten between different tracer injections.
Figure 16 shows cases where the density of the same cortiover a factor of ten between different tracer injections.
Figure 1*b* shows cases where the density of the same corti-
cocortical connection varies over a factor of 100 between over a factor of ten between different tracer injections.
Figure 1b shows cases where the density of the same corti-
cocortical connection varies over a factor of 100 between
different tracer injections. In both the thelam Figure 1b shows cases where the density of the same corticocortical connection varies over a factor of 100 between different tracer injections. In both the thalamocortical and corticocortical cases the mean densities of cocortical connection varies over a factor of 100 between
different tracer injections. In both the thalamocortical
and corticocortical cases, the mean densities of the
stronger connections may be over 1000 times that of th different tracer injections. In both the thalamocortical
and corticocortical cases, the mean densities of the
stronger connections may be over 1000 times that of the
weaker connections and corticocortical cases, the mean densities of the stronger connections may be over 1000 times that of the weaker connections.

(b) *Relationship between mean and standard deviation of connection density*

deviation of connection density
To explore the relationship between the variability of connections and their mean density, we performed a

igure 2. Relationship between mean and standard deviation of thalamocortical and corticocortical connection density. The igure 2. Relationship between mean and standard deviation of thalamocortical and corticocortical connection density. The
ertical axes show log standard deviation of the proportion of labelled neurons. The horizontal axes s igure 2. Relationship between mean and standard deviation of thalamocortical and corticocortical connection density. The ertical axes show log standard deviation of the proportion of labelled neurons. The horizontal axes ertical axes show log standard deviation of the proportion of labelled neurons. The horizontal axes show log mean proportion of
the led neurons. (*a*) and (*c*) show raw data from inter- and within-individual cases, respe belled neurons. (*a*) and (*c*) show raw data from inter- and within-individual cases, respectively. Each point was computed from wo or more tracer injections. The within-individual data (*c*) is more scattered because sa wo or more tracer injections. The within-individual data (c) is more scattered because sample sizes were never greater than two.
The solid and dotted lines show the relationship between mean and standard deviation for sa The solid and dotted lines show the relationship between mean and standard deviation for samples from an exponential and a coisson distribution, respectively. As connection data were scaled (see §2), we also scaled the da Foisson distribution, respectively. As connection data were scaled (see §2), we also scaled the data used to compute the lines for exponential and Poisson. The scaling process reduces estimates of variability for strong c exponential and Poisson. The scaling process reduces estimates of variability for strong connections. (b) and (d) show
expression lines $(\pm 1 \text{ s.e.})$ for inter-individual and for within-individual data, respectively. The expression lines $(\pm 1 \text{ s.e.})$ for inter-individual and for within-individual data, respectively. The gradient of the regression for pricocortical data is higher than that for thalamocortical data (see also table 2). Stro

preliminary regression analysis of standard deviation reliminary regression analysis of standard deviation
ersus mean for thalamocortical and corticocortical
connections Densities vary over several orders of magnireliminary regression analysis of standard deviation
ersus mean for thalamocortical and corticocortical
onnections. Densities vary over several orders of magni-
de so we used the logs of the mean and standard devia-Tersus mean for thalamocortical and corticocortical pointections. Densities vary over several orders of magni-
and the logs of the mean and standard devia-
and W_e distinguished within-individual statistics (two Jonnections. Densities vary over several orders of magni-
lade, so we used the logs of the mean and standard devia-
on. We distinguished within-individual statistics (two ide, so we used the logs of the mean and standard devia-
on. We distinguished within-individual statistics (two
istinguishable tracer injections in the same area in the
area in the same arimal) from inter-individual stati on. We distinguished within-individual statistics (two
istinguishable tracer injections in the same area in the
ame animal) from inter-individual statistics (no more
an one tracer denosit in any animal) Figure 2 istinguishable tracer injections in the same area in the
ame animal) from inter-individual statistics (no more
an one tracer deposit in any animal). Figure 2
omnares thalamic and cortical data. Figure 3 compares amic animal) from inter-individual statistics (no more tan one tracer deposit in any animal). Figure 2 ompares thalamic and cortical data. Figure 3 compares then and within individual data. an one tracer deposit in any
ompares thalamic and cortical data.
There and within-individual data. ompares thalamic and cortical data. Figure 3 compares units for the unce
ter- and within-individual data.
Because of possible sampling bias and scaling bias in densities (figure 3).

ter- and within-individual data.

Decause of possible sampling bias and scaling bias in

omputing standard deviation (see $\S 3(e)$), the uncor-

eted regression analyses in figures 2 and 3 must be Because of possible sampling bias and scaling bias in
omputing standard deviation (see $\S 3(e)$), the uncor-
eted regression analyses in figures 2 and 3 must be
reated with caution However, the figures show several omputing standard deviation (see $\S 3(e)$), the uncor-
ected regression analyses in figures 2 and 3 must be
cated with caution. However, the figures show several
shust features of the data that we consider briefly here ected regression analyses in figures 2 and 3 must be reated with caution. However, the figures show several obust features of the data that we consider briefly here nd return to later. pbust features of the data that we consider briefly here

First, for stronger connections (more than 1% of First, for stronger connections (more than 1% of labelled neurons, figure 2), thalamocortical variability is lower than corticocortical variability. The regressions First, for stronger connections (more than 1% of labelled neurons, figure 2), thalamocortical variability is lower than corticocortical variability. The regressions suggest however that the relationship may be reversed labelled neurons, figure 2), thalamocortical variability is
lower than corticocortical variability. The regressions
suggest, however, that the relationship may be reversed
for very weak connections where thalamic projectio for than corticocortical variability. The regressions suggest, however, that the relationship may be reversed for very weak connections where thalamic projections suggest, however, that the relationship may be reversed
for very weak connections where thalamic projections
appear more variable. Second, for both corticocortical
and thalamocortical connections, inter-individual stanfor very weak connections where thalamic projections
appear more variable. Second, for both corticocortical
and thalamocortical connections, inter-individual stan-
dard deviation is moderately higher (roughly 0.3 log appear more variable. Second, for both corticocortical
and thalamocortical connections, inter-individual stan-
dard deviation is moderately higher (roughly 0.3 log
units for the uncorrected data) than within-individual and thalamocortical connections, inter-individual standard deviation is moderately higher (roughly 0.3 log units for the uncorrected data) than within-individual standard deviation across a wide range of connection dard deviation is moderately higher (roughly 0.3 log
units for the uncorrected data) than within-individual
standard deviation across a wide range of connection
densities (figure 3) units for the uncorn
standard deviation a
densities (figure 3).
Third and import standard deviation across a wide range of connection
densities (figure 3).
Third, and importantly, log standard deviation connec-

densities (figure 3).
Third, and importantly, log standard deviation connec-
tion density is roughly proportional to log mean connec-
tion density over several orders of magnitude (figures 2) Third, and importantly, log standard deviation connection density is roughly proportional to log mean connection density over several orders of magnitude (figures 2 and 3 table 2). The lines superimposed on the raw data tion density is roughly proportional to log mean connection density over several orders of magnitude (figures 2 and 3, table 2). The lines superimposed on the raw data points represent the relationships between mean and tion density over several orders of magnitude (figures 2 and 3, table 2). The lines superimposed on the raw data points represent the relationships between mean and

BIOLOGICAL SCIENCES

THE ROYAI

PHILOSOPHICAL
TRANSACTIONS

ð

Figure 3. Relationship between mean and standard deviation of connection density for within-individual and inter-individual
area. The vertical axes show log standard deviation of the proportion of labelled neurons. The hor igure 3. Relationship between mean and standard deviation of connection density for within-individual and inter-individual
ases. The vertical axes show log standard deviation of the proportion of labelled neurons. The hori igure 3. Relationship between mean and standard deviation of connection density for within-individual and inter-individual
ases. The vertical axes show log standard deviation of the proportion of labelled neurons. The hor ases. The vertical axes show log standard deviation of the proportion of labelled neurons. The horizontal axes show log mean
roportion of labelled neurons. (*a*) and (*c*) show raw thalamic and cortical data, respectively roportion of labelled neurons. (*a*) and (*c*) show raw thalamic and cortical data, respectively. Each point was computed from *w*o or more tracer injections within an individual study. The intra-individual data (*a*) and so or more tracer injections within an individual study. The intra-individual data (a) and (c) are more scattered because sample
zes were never greater than two. The solid and dotted lines show the relationship between me zes were never greater than two. The solid and dotted lines show the relationship between mean and standard deviation for
a mples from an exponential and a Poisson distribution, respectively. As connection data were scale mples from an exponential and a Poisson distribution, respectively. As connection data were scaled (see § 2), we also scaled the ata used to compute the lines for the exponential and Poisson. The scaling process reduces e ata used to compute the lines for the exponential and Poisson. The scaling process reduces estimates of variability for strong
nections. (*b*) and (*d*) show regression lines (\pm 1 s.e.) for inter- and for within-indivi Independent point (*d*) show regres at a show a similar slope to inter-inveportionately lower variability.

BIOLOGICAL SCIENCES

THE ROYAL

PHILOSOPHICAL
TRANSACTIONS ð

> reportionately lower variability.
andard deviation that would be expected from a simple
loisson, process, and, from an exponential distribution andard deviation that would be expected from a simple
poisson process and from an exponential distribution
formes $2a \epsilon$ and $3a \epsilon$). Both of these theoretical lines were andard deviation that would be expected from a simple
poisson process and from an exponential distribution
figures $2a,c$ and $3a,c$). Both of these theoretical lines were
lomputed taking account of scaling bias and this poisson process and from an exponential distribution
figures $2a,c$ and $3a,c$). Both of these theoretical lines were
jomputed taking account of scaling bias, and this
values why their slopes decline for strong connections figures $2a,c$ and $3a,c$). Both of these theoretical lines were

> bomputed taking account of scaling bias, and this

> splains why their slopes decline for strong connections. It is element of scaling bias, and this explains why their slopes decline for strong connections.

> It is clear that the Poisson model predicts unrealistically

> It is connection variability. In contrast, the line represent $\sum_{\text{L}}^{\text{xplains why their slopes decline for strong connections.}$ is clear that the Poisson model predicts unrealistically we connection variability. In contrast, the line representing samples drawn from an exponential distribution w connection variability. In contrast, the line repre-
enting samples drawn from an exponential distribution
rovides a good description of the relationship between
arishility and mean enting samples drawn
rovides a good descri
ariability and mean.

(c) *Relationship between mean and median connection density*

connection density does not look like that predicted by a bisson process, but does resemble an exponential. Iowever, figures 2 and 3 could, in principle, show that

connection densities follow a normal distribution in which the standard deviation scales in proportion to the mean.
the standard deviation scales in proportion to the mean.
Normally, distributed, data, are, not, skewed, A, robus

the standard deviation scales in proportion to the mean.
Normally distributed data are not skewed. A robust measure of skew, particularly when sample size is small, is the ratio of median to mean. This ratio will be centred on measure of skew, particularly when sample size is small, is
the ratio of median to mean. This ratio will be centred on
one for samples drawn from a normal distribution. It will
be less than one for positively skewed data a the ratio of median to mean. This ratio will be centred on
one for samples drawn from a normal distribution. It will
be less than one for positively skewed data and more than
one for negatively skewed data one for samples drawn from a no
be less than one for positively ske
one for negatively skewed data.
To explore the samples of The set of connectively skewed data and more than
the samples of connection data, we
connection data, we
connect the samples of connection data, we
connected the ratio of sample median to sample mean for

(c) **Relationship between mean and median** size necessary for mean and median to be different). This
connection density
The relationship between mean and standard deviation unfortunately, excluded all within-individual sam one for negatively skewed data.
To explore the samples of connection data, we calculated the ratio of sample median to sample mean for
all sample sizes greater than two (the minimum sample To explore the samples of connection data, we calculated the ratio of sample median to sample mean for all sample sizes greater than two (the minimum sample size necessary for mean and median to be different). This calculated the ratio of sample median to sample mean for
all sample sizes greater than two (the minimum sample all sample sizes greater than two (the minimum sample size necessary for mean and median to be different). This included the vast majority of inter-individual samples but, unfortunately excluded all within-individual sampl size necessary for mean and median to be different). This
included the vast majority of inter-individual samples but,
unfortunately, excluded all within-individual samples.
Eigure 4 shows that with the exception of one dat included the vast majority of inter-individual samples but,
unfortunately, excluded all within-individual samples.
Figure 4 shows that, with the exception of one data point
(representing data from a single study of thalamo Figure 4 shows that, with the exception of one data point (representing data from a single study of thalamocortical connections, see $\S 4$), the median to mean ratio is

Table 2. *Coefficients for linear regression between log standard*
eviation (s) and log mean (x) given by the equation logs *diation* (*s*) *and log mean* (\bar{x}) *given by the equation* log*s* $= k \log \bar{x} + c$ *, where k is the slope and c is the intercept* $\left(\frac{S}{T}\right)$ and $\log \frac{S}{T}$ table and $\left(\frac{S}{T}\right)$ and $\log S$
= $k \log \frac{S}{T} + c$, where k is the slope and c is the intercept
The table also shows the standard error in the slope and
tercent estimates and the goodness of

BIOLOGICAL SCIENCES

BIOLOGICAL
SCIENCES **CIENCES**

THE ROYAL

PHILOSOPHICAL
TRANSACTIONS

Figure 1. The state of the state and the state intercept
The table also shows the standard error in the slope and
tercept estimates, and the goodness of fit, R^2 , of the regression.
The expected standard deviation for a itercept estimates, and the goodness of fit, R^2 , of the regression. The table also shows the standard error in the slope and
itercept estimates, and the goodness of fit, R^2 , of the regression.
The expected standard deviation for any mean density is given
 $y = \log 10^{(c+kx)}$ (a) Results of itercept estimates, and the goodness of fit, R^2 , of the regression.
The expected standard deviation for any mean density is given
 $y = log 10^{(c+kx)}$. (*a*) Results of regressions of raw data in
thich estimates of standard The expected standard deviation for any mean density is given
 $y = log 10^{(e+k\bar{x})}$. (a) Results of regressions of raw data in

thich estimates of standard deviation have not been corrected

Nur sampling bias or scaling bias $f(x) = \log 10^{(c+k\tilde{x})}$. (*a*) Results of regressions of raw data in thich estimates of standard deviation have not been corrected or scaling bias; (*b*) results of regressions of orrected data where estimates of standard d - hich estimates of standard deviation have not been corrected
or sampling bias or scaling bias; (b) results of regressions of
orrected data where estimates of standard deviation have been
orrected for sampling bias and s For sampling bias or scaling bias; (b) results or sprected data where estimates of standard deviation or sected for sampling bias and scaling bias.)

significantly less than one, and is closer to 0.7. Therefore,
the distribution of connection densities is highly nongnificantly less than one, and is closer to 0.7. Therefore,
ne distribution of connection densities is highly non-
ormal and strongly positively skewed gnificantly less than one, and is closer
ne distribution of connection densities
ormal and strongly positively skewed. **(d)** *The distribution of connection densities*

The results so far force us to reject two candidate distri-(d) The distribution of connection densities
The results so far force us to reject two candidate distri-
utions that could, in principle, describe the spread of
orticocontical and thalamocortical connection densities The results so far force us to reject two candidate distriutions that could, in principle, describe the spread of orticocortical and thalamocortical connection densities.
First, the ratio of mean to median shows that the d utions that could, in principle, describe the spread of orticocortical and thalamocortical connection densities.

irst, the ratio of mean to median shows that the distribu-

on is bighly non-normal (with the possible excep orticocortical and thalamocortical connection densities.

irst, the ratio of mean to median shows that the distribu-

on is highly non-normal (with the possible exception of irst, the ratio of mean to median shows that the distribu-
on is highly non-normal (with the possible exception of
nalamic projections to MS, see $\S 4$). Second, variability is
no high to be accounted for by a simple Pois on is highly non-normal (with the possible exception of nalamic projections to MS, see $\S 4$). Second, variability is oo high to be accounted for by a simple Poisson model.
The frequency distribution that resembles our da alamic projections to MS, see $\S 4$). Second, variability is
the physical form that resembles our data in
One frequency distribution that resembles our data in
rms of skew is the geometrical distribution. When the

to high to be accounted for by a simple Poisson model.
One frequency distribution that resembles our data in
terms of skew is the geometrical distribution. When the mean number of events (e.g. labelled neurons) is large, as Figures of skew is the geometrical distribution. When the earn number of events (e.g. labelled neurons) is large, as all but the weakest of anatomical connections, the experiments distribution approximates its continuous The number of events (e.g. labelled neurons) is large, as
 $\frac{1}{1}$ all but the weakest of anatomical connections, the

eometric distribution approximates its continuous
 $\frac{1}{1}$ alogue the exponential or Boltzmann dis and the weakest of anatomical connections, the exponential distribution approximates its continuous analogue, the exponential or Boltzmann distribution. The exponential distribution is defined in equation (4) where exponential distribution approximates its continuous

analogue, the exponential or Boltzmann distribution. The

sponential distribution is defined in equation (4), where a nalogue, the exponential or Boltzmann distribution. The exponential distribution is defined in equation (4), where the probability of obtaining a score *x* is $p(x)$ and μ is the spean of the distribution **Exponential distribution is
The probability of obtainin
Frean of the distribution.**

$$
\mathcal{Q}(x) = \frac{1}{\mu} e^{-x/\mu}.
$$
\n(4)

Figure 4 shows the ratio of median to mean for samples rawn from an exponential distribution for a range of ample sizes (dashed line in figure 4). Although the igure 4 shows the ratio of median to mean for samples
rawn from an exponential distribution for a range of
ample sizes (dashed line in figure 4). Although the
naller experimental samples are more skewed than rawn from an exponential distribution for a range of
ample sizes (dashed line in figure 4). Although the
naller experimental samples are more skewed than
and lower show a symptom is also that the
lower that the ample sizes (dashed line in figure 4). Although the naller experimental samples are more skewed than ∂ ould be expected for an exponential, it is clear that the nedian to mean ratio of the connection data is much maller experimental samples are more skewed than
 \overline{a} ould be expected for an exponential, it is clear that the

redian to mean ratio of the connection data is much

loser to an exponential than a normal distribution If yould be expected for an exponential, it is clear than edian to mean ratio of the connection data is not loser to an exponential than a normal distribution. redian to mean ratio of the connection data is much
seer to an exponential than a normal distribution.
For the next section of this paper and in Appendix A,
redont the exponential distribution as a simple 'working

loser to an exponential than a normal distribution.
For the next section of this paper and in Appendix A,
 ve adopt the exponential distribution as a simple 'working
rodel', of the frequency distribution of connection For the next section of this paper and in Appendix A, χ adopt the exponential distribution as a simple 'working nodel' of the frequency distribution of connection *Phil. Trans. R. Soc. Lond.* B (2000) *Phil. Trans. R. Soc. Lond.* B (2000)

densities. However, we qualify our use of the exponential
for several reasons. First, the exponential approximation densities. However, we qualify our use of the exponential
for several reasons. First, the exponential approximation
is not a perfect description of the variability that we find densities. However, we qualify our use of the exponential
for several reasons. First, the exponential approximation
is not a perfect description of the variability that we find.
This is shown by the fact that the slopes an for several reasons. First, the exponential approximation
is not a perfect description of the variability that we find.
This is shown by the fact that the slopes and intercepts of the regressions between standard deviation and mean are This is shown by the fact that the slopes and intercepts of
the regressions between standard deviation and mean are
not one and zero, the values predicted for an exponential
 $(table-2)$ As a result, the exponential underestim the regressions between standard deviation and mean are
not one and zero, the values predicted for an exponential
(table 2). As a result, the exponential underestimates
variability for the very weak connections and overest not one and zero, the values predicted for an exponential (table 2). As a result, the exponential underestimates variability for the very weak connections and overestimates variability for very strong connections. Second (table 2). As a result, the exponential underestimates variability for the very weak connections and overestimates variability for very strong connections. Second, variability for the very weak connections and overestimates variability for very strong connections. Second, figure 4 shows that the connection data appear even more skewed than predicted by an exponential distribution mates variability for very strong connections. Second,
figure 4 shows that the connection data appear even more
skewed than predicted by an exponential distribution.
This feature would be expected under a geometrical figure 4 shows that the connection data appear even more
skewed than predicted by an exponential distribution.
This feature would be expected under a geometrical
distribution (of which the exponential is the continuous skewed than predicted by an exponential distribution.
This feature would be expected under a geometrical
distribution (of which the exponential is the continuous
analogue) for weak connections where u^2 is not much This feature would be expected under a geometrical
distribution (of which the exponential is the continuous
analogue) for weak connections where μ^2 is not much
larger than μ the mean number of labelled neurons 2 is distribution (of which the exponential is the continuous
analogue) for weak connections where μ^2 is not much
larger than μ , the mean number of labelled neurons.
These factors lead us to suggest that a more general analogue) for weak connections where μ^2 is not much
larger than μ , the mean number of labelled neurons.
These factors lead us to suggest that a more general class
of frequency distributions known as the negative bi larger than μ , the mean number of labelled neurons.
These factors lead us to suggest that a more general class
of frequency distributions known as the negative binomial (of which the geometrical distribution is a special case) probably provides a better description of the distribution (of which the geometrical distribution is a special case)
probably provides a better description of the distribution
of connection densities (see $\S 4$). Negative binomials are
attractive as they arise under hierarchical probably provides a better description of the distribution
of connection densities (see §4). Negative binomials are
attractive, as they arise under hierarchical generative
models (Solomon 1983: Casella & Berger 1990) whic of connection densities (see $\S 4$). Negative binomials are
attractive, as they arise under hierarchical generative
models (Solomon 1983; Casella & Berger 1990), which
might apply if a range of random processes are involv attractive, as they arise under hierarchical generative models (Solomon 1983; Casella & Berger 1990), which might apply if a range of random processes are involved in models (Solomon 1983; Casella & Berger 1990), which
might apply if a range of random processes are involved in
the measurement of connection strengths with connection
probabilities drawn from a continuous distribution. Thi might apply if a range of random processes are involved in
the measurement of connection strengths with connection
probabilities drawn from a continuous distribution. This
would occur for example in a patchy cortical area the measurement of connection strengths with connection
probabilities drawn from a continuous distribution. This
would occur, for example, in a patchy cortical area
containing domains that varied in their connection densiprobabilities drawn from a continuous distribution. This would occur, for example, in a patchy cortical area containing domains that varied in their connection densiwould occur, for example, in a patchy cortical area
containing domains that varied in their connection densi-
ties. While attractive, we do not develop a negative bino-
mial model here for two reasons. First, it is not cle containing domains that varied in their connection densi-
ties. While attractive, we do not develop a negative bino-
mial model here for two reasons. First, it is not clear that
the negative binomial distribution offers a ties. While attractive, we do not develop a negative binomial model here for two reasons. First, it is not clear that
the negative binomial distribution offers a sufficient
improvement or substantially alters our results o mial model here for two reasons. First, it is not clear that
the negative binomial distribution offers a sufficient
improvement, or substantially alters our results or concluthe negative binomial distribution offers a sufficient
improvement, or substantially alters our results or conclu-
sions. Second, a large amount of quantitative data are
required to distinguish between competing models. Su improvement, or substantially alters our results or conclusions. Second, a large amount of quantitative data are
required to distinguish between competing models. Such
data should come from a nurnose-designed study carried sions. Second, a large amount of quantitative data are
required to distinguish between competing models. Such
data should come from a purpose-designed study carried
out with consistent methods in a single laboratory and is required to distinguish between competing models. Such
data should come from a purpose-designed study carried
out with consistent methods in a single laboratory, and is data should come from a purpose-designed study carried beyond the quality of the data that are currently available.

t with consistent methods in a single laboratory, and is
yond the quality of the data that are currently available.
The implications of an exponential distribution of
prection densities are as follows. First, methods of The implications of an exponential distribution of connection densities are as follows. First, methods of inferential statistics based on the assumption of a normal distribution simply do not apply Second connection data connection densities are as follows. First, methods of inferential statistics based on the assumption of a normal distribution simply do not apply. Second, connection data are highly skewed and highly variable so rather la inferential statistics based on the assumption of a normal distribution simply do not apply. Second, connection data
are highly skewed and highly variable so rather large
amounts of data are necessary for confident estimates of
connection density and/or variability (see Annendix A are highly skewed and highly variable so rather large
amounts of data are necessary for confident estimates of
connection density and/or variability (see Appendix A,
and figures 8 and 9) Third and more decentively the amounts of data are necessary for confident estimates of
connection density and/or variability (see Appendix A,
and figures 8 and 9). Third, and more deceptively, the
standard measure of variability sample standard connection density and/or variability (see Appendix A, and figures 8 and 9). Third, and more deceptively, the standard measure of variability, sample standard deviation, systematically underestimates population stanstandard measure of variability, sample standard
deviation systematically underestimates population standard deviation when given small samples drawn from
highly skewed distributions such as the exponential deviation, systematically underestimates population standard deviation when given small samples drawn from
highly skewed distributions such as the exponential
(figure 8b) This bias depends on sample size so estimates dard deviation when given small samples drawn from
highly skewed distributions such as the exponential
(figure 8*b*). This bias depends on sample size, so estimates
of variability based on small samples will be lower than highly skewed distributions such as the exponential (figure 8b). This bias depends on sample size, so estimates of variability based on small samples will be lower than (figure $8b$). This bias depends on sample size, so estimates
of variability based on small samples will be lower than
estimates based on large samples. We consider sampling
bias below and in greater detail in Appendix $\$ of variability based on small samples will be lower than
estimates based on large samples. We consider sampling
bias below and in greater detail in Appendix A (see also
figure $8b$) estimates ba
bias below a
figure 8*b*).

(e) *Sampling bias and scaling bias*

(e) **Sampling bias and scaling bias**
We performed a Monte Carlo simulation to assess the
ect of sampling bias on the standard deviation of (e) **Sampling bias and scaling bias**
We performed a Monte Carlo simulation to assess the
effect of sampling bias on the standard deviation of
samples drawn from exponentially distributed data. We We performed a Monte Carlo simulation to assess the effect of sampling bias on the standard deviation of samples drawn from exponentially distributed data. We took 10,000 samples in a range of sample sizes (from two effect of sampling bias on the standard deviation of
samples drawn from exponentially distributed data. We
took 10 000 samples in a range of sample sizes (from two
to ten) from an exponentially distributed population of samples drawn from exponentially distributed data. We
took 10 000 samples in a range of sample sizes (from two
to ten) from an exponentially distributed population of
random numbers with a population mean of one and took 10 000 samples in a range of sample sizes (from two
to ten) from an exponentially distributed population of
random numbers with a population mean of one and
standard deviation of one Sampling bias in standard to ten) from an exponentially distributed population of random numbers with a population mean of one and standard deviation of one. Sampling bias in standard deviation was therefore equal to the mean value of sample

BIOLOGICAL CIENCES

ROYA

THE

PHILOSOPHICAL
TRANSACTIONS

BIOLOGICAL SCIENCES

sample size
igure 4. The median proportion of labelled neurons is systematically less than the mean proportion of labelled neurons. The
ertical axis shows the ratio of median to mean connection density: a robust measure of igure 4. The median proportion of labelled neurons is systematically less than the mean proportion of labelled neurons. The
- ertical axis shows the ratio of median to mean connection density; a robust measure of skew. The igure 4. The median proportion of labelled neurons is systematically less than the mean proportion of labelled neurons. The
ertical axis shows the ratio of median to mean connection density; a robust measure of skew. The h Frequence intervals of median to mean connection density; a robust measure of skew. The horizontal axis shows sample \geq (the number of tracer injections; one per animal) from which the median to mean ratio for each con ze (the number of tracer injections; one per animal) from which the median to mean ratio for each connection was compute
rror bars show the 95% confidence intervals of the mean ratio of sample median to sample mean. The d median to mean ratio for samples drawn from a normal distribution. The dashed and dotted line is the expected nedian to mean ratio for samples drawn from an exponential distribution, which tends towards log_e2 (dashed li spected median to mean ratio for samples drawn from a normal distribution. The dashed and dotted line is the expected
redian to mean ratio for samples drawn from an exponential distribution, which tends towards $\log_e 2$ (d not in the mean ratio for samples drawn from an exponential distribution, which tends towards $log_e 2$ (dashed line) when sample ze is large. In general, the empirically derived skew is closer to that expected by sampling f ze is large. In general, the empirically derived skew is closer to that expected by sampling from an exponential than from a
ormal distribution. In fact, the data are even more skewed than an exponential distribution (see ormal distribution. In fact, the data are even more skew
y an asterisk, is an obvious outlier. These data, which ap
udy of the thalamic projections to MS cortex (see $\S 4$).

andard deviation for each sample size (see Appendix A, alid line in figure $8b$) andard deviation for explicit line in figure $8b$).
Sampling hias was subbid line in figure $8b$).
Sampling bias was substantial for small samples. For

bid line in figure $8b$).
Sampling bias was substantial for small samples. For
xample, with sample sizes of two, three and four, sample
andard deviation was only 0.70, 0.80 and 0.84 times the Sampling bias was substantial for small samples. For
xample, with sample sizes of two, three and four, sample
andard deviation was only 0.70, 0.80 and 0.84 times the
current population standard deviation. We corrected the xample, with sample sizes of two, three and four, sample
andard deviation was only 0.70, 0.80 and 0.84 times the
rue population standard deviation. We corrected the
resurses of variability computed from anatomical data andard deviation was only 0.70, 0.80 and 0.84 times the
rue population standard deviation. We corrected the
reasures of variability computed from anatomical data
v dividing the sample standard deviation by sampling rue population standard deviation. We corrected the reasures of variability computed from anatomical data
y dividing the sample standard deviation by sampling
is for the appropriate sample size reasures of variability computed from
y dividing the sample standard devalues in the appropriate sample size.
Scaling measures of connection den y dividing the sample standard deviation by sampling
ias for the appropriate sample size.
Scaling measures of connection density, by dividing cell

ounts for individual connections by the total count, also educes estimates of the variability of connections. The caling bias is particularly severe for strong connections because these covary strongly with the total count. scaling bias is particularly severe for strong connections
cause these covary strongly with the total count.
caling bias is intuitively understandable if one thinks of
very strong connection that contains nearly all the ecause these covary strongly with the total count.

caling bias is intuitively understandable if one thinks of

very strong connection that contains nearly all the

belled neurons for such a connection the proportion of caling bias is intuitively understandable if one thinks of
very strong connection that contains nearly all the
belled neurons. For such a connection, the proportion of
axial labelled neurons will always be close to one wha very strong connection that contains nearly all the

bibelled neurons. For such a connection, the proportion of

bital labelled neurons will always be close to one, what-

ver the absolute variations in its density. Theref belled neurons. For such a connection, the proportion of

the labelled neurons will always be close to one, what-

ver the absolute variations in its density. Therefore, this

onnection will appear to have a very low level It also also also also will always be close to one, what-
yer the absolute variations in its density. Therefore, this
onnection will appear to have a very low level of varia-
iity across cases Solute variations in its density. Therefore, this onnection will appear to have a very low level of varia-
and littly across cases. nnection will appear to have a very low level of varia-
ity across cases.
Scaling bias in estimates of variability occurs whenever
dividual measures are divided by a summed measure

ility across cases.

Scaling bias in estimates of variability occurs whenever

idividual measures are divided by a summed measure

ith which they covary but the details of the bias vary with Scaling bias in estimates of variability occurs whenever
idividual measures are divided by a summed measure
ith which they covary, but the details of the bias vary with
the nature of the covariance between individual measu Individual measures are divided by a summed measure
Lith which they covary, but the details of the bias vary with
 \overline{O} he nature of the covariance between individual measures The vector of the total. To obtain an accurate estimate of scaling bias and the total. To obtain an accurate estimate of scaling bias a curate discussion of scaling bias If the covariance between individual measures

and the total. To obtain an accurate estimate of scaling bias

i our data, we performed a Monte Carlo simulation that

sed distributions that were very similar to those found nd the total. To obtain an accurate estimate of scaling bias
1 our data, we performed a Monte Carlo simulation that
sed distributions that were very similar to those found in
the experimental data. The model is outlined in 5). Here S_c and R_c are random variables that represent,

respectively, the proportion and number of neurons labelled via connection *^c*. In line with the anatomical data, respectively, the proportion and number of neurons
labelled via connection ϵ . In line with the anatomical data,
the distribution of R_{ϵ} is exponential. R_{θ} represents the
number of neurons labelled by all the o labelled via connection ϵ . In line with the anatomical data,
the distribution of R_{ϵ} is exponential. R_{θ} represents the
number of neurons labelled by all the other connections. As
 R is the consequence of addi the distribution of R_c is exponential. R_o represents the number of neurons labelled by all the other connections. As R_o is the consequence of adding a large number of exponentially distributed random variables (i.e. number of neurons labelled by all the other connections. As R_g is the consequence of adding a large number of exponentially distributed random variables (i.e. the other connections), we assume that it is normally distributed.

$$
S_c = \frac{R_c}{R_c + R_o}.\tag{5}
$$

We ran our simulations with the mean total number of labelled neurons $T = R_c + R_o = 10000$. Therefore, the We ran our simulations with the mean total number of labelled neurons $T = R_c + R_o = 10000$. Therefore, the mean of $R_o = 10000 - R_c$. We found that scaling bias is only weakly dependent on total neuron number. The labelled neurons $T=R_c+R_o=10000$. Therefore, the
mean of $R_o=10000-R_c$. We found that scaling bias is
only weakly dependent on total neuron number. The
value of T that we have chosen produces results that are mean of $R_e = 10000 - R_e$. We found that scaling bias is
only weakly dependent on total neuron number. The
value of *T* that we have chosen produces results that are
representative for the range of values of *T* (roughly 100 only weakly dependent on total neuron number. The value of T that we have chosen produces results that are representative for the range of values of T (roughly 1000 to 20.000 labelled neurons) present in the data value of T that we have chosen produces results that are
representative for the range of values of T (roughly 1000
to 20 000 labelled neurons) present in the data.
We took a large number of large samples in a range of presentative for the range of values of T (roughly 1000
20 000 labelled neurons) present in the data.
We took a large number of large samples in a range of
nnection strengths (mean R was from 1 to 8000 labelled

the experimental data. The model is outlined in equation that the experimental data. The model is outlined in equation in equation be straight, with slopes of 1 and 0.5, respectively.
See experimental data. The model is o connection strengths (mean *^R^c* was from 1 to 8000 labelled neurons, and mean R_{α} was from 9999 to 2000 labelled connection strengths (mean R_c was from 1 to 8000 labelled
neurons, and mean R_o was from 9999 to 2000 labelled
neurons) to represent cell counts for connection c and all the
other connections We then computed *S* (eq neurons, and mean R_o was from 9999 to 2000 labelled
neurons) to represent cell counts for connection ϵ and all the
other connections. We then computed S_c (equation (6)) and
the standard deviation of S for each mean neurons) to represent cell counts for connection ϵ and all the other connections. We then computed S_{ϵ} (equation (6)) and the standard deviation of S_{ϵ} for each mean connection strength. The results of the simu other connections. We then computed S_c (equation (6)) and
the standard deviation of S_c for each mean connection
strength. The results of the simulation (and of an equivalent
simulation for Poisson data) are shown by t the standard deviation of S_c for each mean connection
strength. The results of the simulation (and of an equivalent
simulation for Poisson data) are shown by the lines in figures
 $2a c$ and $3a c$. In the absence of scali strength. The results of the simulation (and of an equivalent
simulation for Poisson data) are shown by the lines in figures
 $2a,c$ and $3a,c$. In the absence of scaling bias, these lines
would be straight, with slopes of 1 simulation for Poisson data) are shown by the lines in figures 2*a*,*c* and 3*a*,*c*. In the absence of scaling bias, these lines would be straight, with slopes of 1 and 0.5, respectively.
Equivalent lines for the Poisson and exponential, correcting for scaling bias, appearin figures would be straight, with slopes of 1 and 0.5, if
Equivalent lines for the Poisson and exponential
for scaling bias, appear in figures $5a,c$ and $6a,c$.

halamocortical connections, although the situation may be reversed for weak connections.
A comparison of figures 2 and 3 with figures 5 and 6 the standard deviation the standard deviation. Both biases must be corrected to
provide good estimates of the true relationship between igure 5. Relationship between the mean and standard deviation of thalamocortical and corticocortical connection density when igure 5. Relationship between the mean and standard deviation of thalamocortical and corticocortical connection density whe impling bias and scaling bias in standard deviation are corrected. The vertical axes show the log igure 5. Relationship between the mean and standard deviation of thalamocortical and corticocortical connection density when
ampling bias and scaling bias in standard deviation are corrected. The vertical axes show the lo impling bias and scaling bias in standard deviation are corrected. The vertical axes show the log of the standard deviation of
reproportion of labelled neurons. The horizontal axes show the log of the mean proportion of l interpreted data points for inter- and within-individual cases, respectively. Each point was computed from two or more tracer
is perfected data points for inter- and within-individual cases, respectively. Each point was c ijections within an individual study. The solid and dotted lines show the relationship between mean and standard deviation for for individual study. The solid and dotted lines show the relationship between mean and standard deviation is
imples drawn from exponential and Poisson distributions, respectively. (b) and (d) show regression lines (± 1 that the method is drawn from exponential and Poisson distributions, respectively. (*b*) and (*d*) show regression lines (± 1 s.e.) for inter-
in that individual data, respectively. The gradient of the regression for c ralamocortical data (see also table 2). Strong corticocortical connections tend to be more variable in density than strong

BIOLOGICAL SCIENCES

THE ROYA

PHILOSOPHICAL
TRANSACTIONS

p

A comparison of figures 2 and 3 with figures 5 and 6
all pows that scaling bias is substantial for strong connections.
for connections that account for 25% of the total number A comparison of figures 2 and 3 with figures 5 and 6
pows that scaling bias is substantial for strong connections.
or connections that account for 25% of the total number
of labelled neurons scaling bias will reduce standa Now that scaling bias is substantial for strong connections.

For connections that account for 25% of the total number

(abbelled neurons, scaling bias will reduce standard devia-

(b) connections to reduce the property o For connections that account for 25% of the total number

flabelled neurons, scaling bias will reduce standard devia-

on estimates to roughly 0.66 of their true value. We

on puted a correction factor corresponding to Flabelled neurons, scaling bias will reduce standard devia-
on estimates to roughly 0.66 of their true value. We
pomputed a correction factor corresponding to the differ-
nee between the log standard deviation of scaling-b on estimates to roughly 0.66 of their true value. We

somputed a correction factor corresponding to the differ-

nce between the log standard deviation of scaling-biased

xponential data (figures 2 and 3) and the log stand omputed a correction factor corresponding to the differ-
nce between the log standard deviation of scaling-biased
xponential data (figures 2 and 3) and the log standard
eviation of unbiased exponential data (figures 5 and nce between the log standard deviation of scaling-biased
exponential data (figures 2 and 3) and the log standard
eviation of unbiased exponential data (figures 5 and 6). We
enabled this factor to the standard deviation es xponential data (figures 2 and 3) and the log standard eviation of unbiased exponential data (figures 5 and 6). We are added this factor to the standard deviation estimates of a connection data (figures 5 and 6) eviation of unbiased exponential data (figures 5 and 6). We
en added this factor to the standard deviation estimates of
 $\frac{1}{2}$ ae connection data (figures 5 and 6).

(f) *Comparison of corticocortical and thalamocortical variability, and of intraand inter-individual variability: corrected data*

caling bias and sampling bias, which both tend to reduce

the standard deviation. Both biases must be corrected to
provide good estimates of the true relationship between
mean and standard deviation connection density. This is the standard deviation. Both biases must be corrected to provide good estimates of the true relationship between
mean and standard deviation connection density. This is
necessary, to reveal differences in corticocortical a provide good estimates of the true relationship between
mean and standard deviation connection density. This is
necessary to reveal differences in corticocortical and thalamocortical connections, and to assess quantitative necessary to reveal differences in corticocortical and
thalamocortical connections, and to assess quantitative
differences in within- and inter-individual variability.
Eigures 5 and 6 show the relationships between mean an thalamocortical connections, and to assess quantitative
differences in within- and inter-individual variability.
Figures 5 and 6 show the relationships between mean and
standard deviation after appropriate correction. The differences in within- and inter-individual variability.
Figures 5 and 6 show the relationships between mean and
standard deviation after appropriate correction. The
results here are qualitatively similar, but quantitative Figures 5 and 6 show the relationships between mean and
standard deviation after appropriate correction. The
results here are qualitatively similar, but quantitatively
different to figures 2 and 3 standard deviation after a
results here are qualitatively
different, to figures 2 and 3.
First strong corticocortical results here are qualitatively similar, but quantitatively
different, to figures 2 and 3.
First, strong corticocortical connections are more vari-

 $\begin{array}{c}\n\text{2}\n\text{2}\n\end{array}$
 $\begin{array}{c}\n-1 \\
\end{array}$

and thalamocortical variability, and of intra-

and inter-individual variability: corrected data deviation $1.5-2$ times greater than equivalent density

The data in figures 2 and 3 are likely to suffer from thalamic conn different, to figures 2 and 3.
First, strong corticocortical connections are more variable than strong thalamocortical connections (figure 5).
For example, corticocortical connections with around First, strong corticocortical connections are more variable than strong thalamocortical connections (figure 5).
For example, corticocortical connections with around 10% of labelled neurons tend to have a standard able than strong thalamocortical connections (figure 5).

For example, corticocortical connections with around
 10% of labelled neurons tend to have a standard

deviation $15-2$ times greater than equivalent density For example, corticocortical connections with around 10% of labelled neurons tend to have a standard deviation $1.5-2$ times greater than equivalent density thalamic connections. This is true for both inter- and within-individual cases. For connections that include deviation 1.5–2 times greater than equivalent density
thalamic connections. This is true for both inter- and
within-individual cases. For connections that include

igure 6. Relationship between the mean and standard deviation of connection density for inter-individual and intra-individual
ases when sampling bias and scaling bias in standard deviation are corrected. The vertical axes igure 6. Relationship between the mean and standard deviation of connection density for inter-individual and intra-individual asses when sampling bias and scaling bias in standard deviation are corrected. The vertical axe ases when sampling bias and scaling bias in standard deviation are corrected. The vertical axes show the log of the standard eviation of the proportion of labelled neurons. The horizontal axes show the log of the mean pro eviation of the proportion of labelled neurons. The horizontal axes show the log of the mean proportion of labelled neurons.
 i) and (*c*) show corrected data points for thalamic and cortical data, respectively. Each po a) and (*c*) show corrected data points for thalamic and cortical data, respectively. Each point was computed from two or more acer injections within an individual study. The solid and dotted lines show the relationship b for the relationship between mean and standard
eviation for samples drawn from exponential and Poisson distributions, respectively. (b) and (d) show regression lines (± 1 s.e.)
or thalamic and for cortical data, respec via tion for samples drawn from exponential and Poisson distributions, respectively. (*b*) and (*d*) show regression lines (± 1 s.e.)
or thalamic and for cortical data, respectively. Within-individual data shows a simi or thalamic and for cortical data, respectively. Within-individual data shows a similar slope to inter-individual data in both $\binom{b}{2}$ and $\binom{d}{b}$ but has a lower intercept (see also table 2). The difference in inte $\binom{1}{3}$) and (d) but has a lower intercept (see also table 2).
orticocortical cases, the standard deviation of within-if intra-individual samples with a comparable mean.

BIOLOGICAL SCIENCES ROYAL PHILOSOPHICAL THE

BIOLOGICAL SCIENCES

THE ROYAL

PHILOSOPHICAL
TRANSACTIONS ð

> f intra-individual samples with a comparable mean.
round 1% of labelled cells, thalamocortical and corticoround 1% of labelled cells, thalamocortical and cortico-
portical connections have very similar variability. For
reak connections (0.1% of labelled cells) inter-individual round 1% of labelled cells, thalamocortical and cortico-
portical connections have very similar variability. For
leak connections $(0.1\%$ of labelled cells) inter-individual
halamic connectivity may be more variable t portical connections have very similar variability. For
leak connections (0.1% of labelled cells) inter-individual
halamic connectivity may be more variable than cortical
connectivity but within-individual variability is s reak connections (0.1% of labelled cells) inter-individual

> halamic connectivity may be more variable than cortical

> ponnectivity, but within-individual variability is similar

> at the similar halamic connectivity may
about that is not that the post of the post of the Second figure 6.000 figure onnectivity, but within-individual variability is similar
or thalamus and cortex.
Second, figure 6 confirms that inter-individual

or thalamus and cortex.
Second, figure 6 confirms that inter-individual ariability is greater than within-individual variability.
Inverge the differences with corrected data (figure 6) are Second, figure 6 confirms that inter-individual ariability is greater than within-individual variability.
Iowever, the differences with corrected data (figure 6) are natter than the estimates based on uncorrected data ariability is greater than within-individual variability.
Iowever, the differences with corrected data (figure 6) are
naller than the estimates based on uncorrected data
figure 3) For example in the region of the corticoc I owever, the differences with corrected data (figure 6) are
naller than the estimates based on uncorrected data
 \perp figure 3). For example, in the region of the corticocortical
 \sim expressions (figure 6*d*) where the egressions (figure 6*d*) where the lines are significantly figure 3). For example, in the region of the corticocortical
different (roughly corresponding connection densities of
 1% and unwards) the ratio of standard deviation of Expressions (figure $6d$) where the lines are significantly ifferent (roughly corresponding connection densities of .1% and upwards), the ratio of standard deviation of within- to inter-individual cases is only in the ran ifferent (roughly corresponding connection densities of $.1\%$ and upwards), the ratio of standard deviation of *i*thin- to inter-individual cases is only in the range of $.13$ to $1:15$ Similarly in the region of the tha .1% and upwards), the ratio of standard deviation of *i*thin- to inter-individual cases is only in the range of :1.3 to 1:1.5. Similarly, in the region of the thalamocortical expressions (figure 6b) where the lines are si rithin- to inter-individual cases is only in the range of :1.3 to 1:1.5. Similarly, in the region of the thalamocortical egressions (figure $6b$) where the lines are significantly egressions (figure $6b$) where the lines are significantly hil. *Trans. R. Soc. Lond.* B (2000)

different (roughly corresponding to connection densities of
0.1% and above), the ratio of standard deviation of withindifferent (roughly corresponding to connection densities of 0.1% and above), the ratio of standard deviation of withindifferent (roughly corresponding to connection).
0.1% and above), the ratio of standard deviation inter-individual ranges from 1:1.3 to 1:1.6.
Variance is the square of standard deviation 0.1% and above), the ratio of standard deviation of withinto inter-individual ranges from 1:1.3 to 1:1.6.
Variance is the square of standard deviation, so stan-

dard deviation ratios can be converted into variance Variance is the square of standard deviation, so standard deviation ratios can be converted into variance ratios. As the ratio of within- to inter-individual variance ranges from $1:1.7$ to $1:2.6$, the ratio of within-in dard deviation ratios can be converted into variance
ratios. As the ratio of within- to inter-individual variance
ranges from 1:1.7 to 1:2.6, the ratio of within-individual
variance to true between-individual variance (i.e ratios. As the ratio of within- to inter-individual variance
ranges from 1:1.7 to 1:2.6, the ratio of within-individual
variance to true between-individual variance (i.e. inter-
individual minus within-individual variance) ranges from 1:1.7 to 1:2.6, the ratio of within-individual
variance to true between-individual variance (i.e. inter-
individual minus within-individual variance), ranges from
1:0.7 to 1:1.6. These values show that both tru variance to true between-individual variance (i.e. inter-

individual minus within-individual variance), ranges from

1:0.7 to 1:1.6. These values show that both true within-

individual factors (local heterogeneity in tra individual minus within-individual variance), ranges from
1:0.7 to 1:1.6. These values show that both true within-
individual factors (local heterogeneity in tracer uptake, 1:0.7 to 1:1.6. These values show that both true within-
individual factors (local heterogeneity in tracer uptake,
experimental error) and true between-individual factors
(experimentic differences hetween animals) contrib individual factors (local heterogeneity in tracer uptake,
experimental error) and true between-individual factors
(systematic differences between animals) contribute
similar amounts of variance to the results of most conne experimental error) and true between-individual factors

(systematic differences between animals) contribute

similar amounts of variance to the results of most connec-

tion tracing experiments (systematic differences between animals) contribute
similar amounts of variance to the results of most connec-
tion tracing experiments.

Third, as with the uncorrected data, the exponential provides a good description of the data, while the Poisson

number labelled neurons
igure 7. A model to account for the experimentally derived distribution of connection densities. (*a*) shows a surface view of a
nall region of a hypothetical cortical area. The area has stringd var s mannoe method is matter and the method in the corrections.

Suppose the correction of a hypothetical cortical area. The area has striped variations in connection density with another structure. Light

and region of a hyp igure 7. A model to account for the experimentally derived distribution of connection densities. (a) shows a surface view of a
nall region of a hypothetical cortical area. The area has striped variations in connection den nall region of a hypothetical cortical area. The area has striped variations in connection density with another structure. Light
ades show weak connections and dark shades show strong connections. Possible locations of sma rades show weak connections and dark shades show strong connections. Possible locations of small tracer injections are marked by
sterisks. (*b*) illustrates the frequency distribution of label density in a distant structu sterisks. (*b*) illustrates the frequency distribution of label density in a distant structure that would result from small injections
and at the locations shown in (*a*). Each small curve represents a Poisson distributio rade at the locations shown in (a) . Each small curve represents a Poisson distribution of connection densities, that would occurre possible to repeatedly inject exactly the same location. (c) shows the frequency distrib (*b*). The dotted line is an exponential with the same location. (*c*) shows the frequency distribution that would result from a series of mall injections at randomly selected asterisks (*a*). The solid line is the sum of nall injections at randomly selected asterisks (a) . The solid line is the sum of the individual Poisson distributions shown in
b). The dotted line is an exponential with the same mean density as the solid line. It would b). The dotted line is an exponential with the same mean density as the solid line. It would be very difficult to distinguish between in exponential (dotted line) and the distribution based on random injections (solid lin ne exponential (dotted line) and the distribution based on random injections (solid line) on the basis of small samples. In fact, if
redistribution of local mean densities within an area was gamma distributed, the combined asterisks. By averaging across all the domains, the distribution of densities from large injections will be very close to a normal.

abstantially underestimates variability in the density of connections.

4. DISCUSSION

(a) *Consequences of variability for neuroanatomical studies*

Our results have implications for interpreting the studies
Our results have implications for interpreting the
urrent neuroanatomical literature, for the design of
properties and for the way Our results have implications for interpreting the
urrent neuroanatomical literature, for the design of
onnection tracing experiments and for the way
connection data are reported The first and most general Furrent neuroanatomical literature, for the design of
onnection tracing experiments and for the way
onnection data are reported. The first and most general
valication is that caution is required when interpreting Indian tracing experiments and for the way

(i) onnection data are reported. The first and most general

(i) propertion is required when interpreting

(i) onnection densities reported in studies with small sample (a) onnection data are reported. The first and most general
proportion is that caution is required when interpreting
ponnection densities reported in studies with small sample
zes. We suggest that sample sizes of around te proposition is that caution is required when interpreting
onnection densities reported in studies with small sample
zes. We suggest that sample sizes of around ten are
cessary for reasonable estimates of the density of

onnection densities reported in studies with small sample
zes. We suggest that sample sizes of around ten are
ecessary for reasonable estimates of the density of
onnections. Our experience indicates that the majority Connection densities reported in studies with small sample
zes. We suggest that sample sizes of around ten are
experience indicates that the majority
onnections. Our experience indicates that the majority
f published studi ecessary for reasonable estimates of the density of onnections. Our experience indicates that the majority f published studies on corticocortical and thalamo-
ortical connections in cats and macagues use samples onnections. Our experience indicates that the majority
f published studies on corticocortical and thalamo-
ortical connections in cats and macaques use samples
at are substantially smaller than ten However, even f published studies on corticocortical and thalamo-

ortical connections in cats and macaques use samples
 Ω at are substantially smaller than ten. However, even

ith sample sizes of ten or more only very large differortical connections in cats and macaques use samples
at are substantially smaller than ten. However, even
ith sample sizes of ten or more, only very large differ-
nees in mean connection density will prove 'significantly' For a substantially smaller than ten. However, even $\dot{\text{ith}}$ sample sizes of ten or more, only very large differences in mean connection density will prove 'significantly' ifferent on a reliable basis (see Annendix A) ith sample sizes of ten or more, only very large differnces in mean connection density will prove 'significantly' ifferent on a reliable basis (see Appendix A).

Second, quantitative connection tracing studies have ended to report scaled data, as such data make it easier

to compare between cases. However, many statistics to compare between cases. However, many statistics
computed directly from scaled data will be misleading.
Therefore scaled data should be supplied with an indicato compare between cases. However, many statistics
computed directly from scaled data will be misleading.
Therefore, scaled data should be supplied with an indica-
tion of the total number of labelled cells so that they ma computed directly from scaled data will be misleading.
Therefore, scaled data should be supplied with an indication of the total number of labelled cells, so that they may
be easily 'unscaled' Therefore, scaled data should be supplied with an indication of the total number of labelled cells, so that they may be easily 'unscaled'. In of the total number of labelled cells, so that they may
easily 'unscaled'.
Third, as connection densities are highly variable,
esenting any single individual's results as representative

be easily 'unscaled'.
Third, as connection densities are highly variable,
presenting any single individual's results as representative
is difficult. This is because most individuals denart consid-Third, as connection densities are highly variable,
presenting any single individual's results as representative
is difficult. This is because most individuals depart consid-
erably from the average pattern and no single i presenting any single individual's results as representative
is difficult. This is because most individuals depart considerably from the average pattern and no single individual
can be very similar to all the others. To re is difficult. This is because most individuals depart considerably from the average pattern and no single individual
can be very similar to all the others. To reflect this
genuine aspect of connection data, the distributio erably from the average pattern and no single individual
can be very similar to all the others. To reflect this
genuine aspect of connection data, the distribution of
connection densities should be quantified (Cherniak can be very similar to all the others. To reflect this
genuine aspect of connection data, the distribution of
connection densities should be quantified (Cherniak
1990) reported and represented in future attempts at genuine aspect of connection data, the distribution of connection densities should be quantified (Cherniak 1990), reported and represented in future attempts at collation and modelling (MacNeil *et al.* 1997) connection densities should be quantified (Cherniak 1990), reported and represented in future attempts at collation and modelling (MacNeil *et al.* 1997).

(b) *Thalamic projections to PMLS*

(b) *Thalamic projections to PMLS*
Both corticocortical and thalamocortical connection
ta typically show a skewed distribution of densities in (b) *Thalamic projections to PMLS*
Both corticocortical and thalamocortical connection
data typically show a skewed distribution of densities in
which the median is substantially lower than the mean Both corticocortical and thalamocortical connection
data typically show a skewed distribution of densities in
which the median is substantially lower than the mean.
The only obvious exceptions are the thalamocortical data typically show a skewed distribution of densities in which the median is substantially lower than the mean.
The only obvious exceptions are the thalamocortical projections to MS from ten tracer deposits made in the which the median is substantially lower than the mean.
The only obvious exceptions are the thalamocortical
projections to MS from ten tracer deposits made in the
laboratory of Dr Payne (asterisk in figure 4). The densities The only obvious exceptions are the thalamocortical
projections to MS from ten tracer deposits made in the
laboratory of Dr Payne (asterisk in figure 4). The densities
of these connections are roughly normally distributed, projections to MS from ten tracer deposits made in the and show very low variability and very little skew.

BIOLOGICAL SCIENCES

THE ROYAI

PHILOSOPHICAL
TRANSACTIONS $\overline{\mathrm{o}}$

> **BIOLOGICAL CIENCES**

ROYA

THE

PHILOSOPHICAL
TRANSACTIONS

BIOLOGICAL
SCIENCES

ROYAL

E **HLL**

PHILOSOPHICAL
TRANSACTIONS

everal factors could account for these 'exceptional' data. everal factors could account for these 'exceptional' data.
The first, and least interesting, is that they represent a satisfical quirk. It is possible that they differ from the everal factors could account for these 'exceptional' data.
The first, and least interesting, is that they represent a atistical quirk. It is possible that they differ from the
ther data just by chance. This would not be al The first, and least interesting, is that they represent a atistical quirk. It is possible that they differ from the ther data just by chance. This would not be altogether urnising as we have computed the median to mean atistical quirk. It is possible that they differ from the ther data just by chance. This would not be altogether urprising, as we have computed the median to mean atios for a large number of samples ther data just by chance. This would
urprising, as we have computed the
atios for a large number of samples.
Second the difference could be d rprising, as we have computed the median to mean
tios for a large number of samples.
Second, the difference could be due to the fact the
udy in Dr. Payne's laboratory took several steps to

atios for a large number of samples.
Second, the difference could be due to the fact the
aboratory took several steps to
dieduce random variability due to the spatial characteris-Second, the difference could be due to the fact the
rudy in Dr Payne's laboratory took several steps to
educe random variability due to the spatial characteris-
is of tracer denosits (MacNeil *et al.* 1997) These are the tics of tracer deposits (MacNeil *et al.* 1997). These are utined in the $\frac{8}{2}$ but in addition to the usual precautions: educe random variability due to the spatial characteris-
ics of tracer deposits (MacNeil *et al.* 1997). These are
utlined in the §2, but in addition to the usual precautions:
i) tracer deposits were limited to a particul ics of tracer deposits (MacNeil *et al.* 1997). These are utlined in the $\S 2$, but in addition to the usual precautions:
i) tracer deposits were limited to a particular region of the visual field representation: (ii) tra utlined in the \S 2, but in addition to the usual precautions:

i) tracer deposits were limited to a particular region of

the visual field representation; (ii) tracer deposits covered
 \bullet reasonable area of the cortex i) tracer deposits were limited to a particular region of
the visual field representation; (ii) tracer deposits covered
the cortex, so avoiding differential
abbelling in subsets of afferent neurons with small or - reasonable area of the cortex, so avoiding differential
□ ibelling in subsets of afferent neurons with small or
□ atchy terminal arborizations (Sherk & Ombrellaro 1988; **patch** in subsets of afferent neurons with small or Payne *et al*. 1991; Shipp & Grant 1991); (iii) all cortical atchy terminal arborizations (Sherk & Ombrellaro 1988;

layne *et al.* 1991; Shipp & Grant 1991); (iii) all cortical

layers were exposed to tracer, so avoiding differential

labelling in subsets of afferent neurons with labelling *i* and 1991; Shipp & Grant 1991); (iii) all cortical labelling in subsets of afferent neurons with different neurons w Quers were exposed to tracer, so avoiding differential
Abelling in subsets of afferent neurons with different
iminar terminations. These factors may be very impor-
ant if the highly variable distribution of connection aminar terminations. These factors may be very imporbelow and ¢gure 7). For patchy connection patterns, ensities is due to local heterogeneity in connectivity (see
elow and figure 7). For patchy connection patterns,
all localized deposits could produce a near exponential
istribution of densities while larger deposits could v elow and figure 7). For patchy connection patterns,
 $\frac{1}{2}$ nall localized deposits could produce a near exponential

istribution of densities, while larger deposits could yield

more normal distribution (see figure 7 and localized deposits could produce a near exponential
istribution of densities, while larger deposits could yield
more normal distribution (see figure 7 and below). This
is because the larger deposits could simultaneousl more normal distribution (see figure 7 and b
i because the larger deposits could simultane
he different connectional subcompartments.
We note that the corticocortical data from because the larger deposits could simultaneously span
e different connectional subcompartments.
We note that the corticocortical data from Dr Payne's
poratory, which are based on the same set of tracer

We note that the corticocortical data from Dr Payne's aboratory, which are based on the same set of tracer injections as the `exceptional' thalamocortical data, bear a aboratory, which are based on the same set of tracer
igections as the 'exceptional' thalamocortical data, bear a
lose resemblance to the other corticocortical data. These
acts could be explained if the corticocortical proj if is a sthe 'exceptional' thalamocortical data, bear a
lose resemblance to the other corticocortical data. These
acts could be explained if the corticocortical projections
 λ MS cortex are more natchy (Montero 1981; Sh lose resemblance to the other corticocortical data. These
test could be explained if the corticocortical projections
> MS cortex are more patchy (Montero 1981; Shipp &
trant 1991) or have coareer patches, than the thalamoacts could be explained if the corticocortical projections
of MS cortex are more patchy (Montero 1981; Shipp &
Frant 1991), or have coarser patches, than the thalamocortical projections (see Sherk 1986). Frant 1991), or have coarser patches, than the thalamorrical projections (see Sherk 1986).
Third, the MS data raise the possibility of a difference
the thalamocortical connectivity of MS cortex and the

ortical projections (see Sherk 1986).
Third, the MS data raise the possibility of a difference
it the thalamocortical connectivity of MS cortex and the
ther areas for which we have data. MS is a relatively Third, the MS data raise the possibility of a difference
i the thalamocortical connectivity of MS cortex and the
ther areas for which we have data. MS is a relatively
w-order visual area, while the others (medial area 6 1 the thalamocortical connectivity of MS cortex and the ther areas for which we have data. MS is a relatively w-order visual area, while the others (medial area 6, inculate and prefrontal cortex) are all higher-order ther areas for which we have data. MS is a relatively
w-order visual area, while the others (medial area 6,
ingulate and prefrontal cortex) are all higher-order
sees The variability in the thalamic connections of these areas, while the others (medial area 6, ingulate and prefrontal cortex) are all higher-order reas. The variability in the thalamic connections of these igher areas is more similar to most of the corticocortical ingulate and prefrontal cortex) are all higher-order
reas. The variability in the thalamic connections of these
igher areas is more similar to most of the corticocortical
onnections than to the thalamic data from MS. This reas. The variability in the thalamic connections of these
igher areas is more similar to most of the corticocortical
onnections than to the thalamic data from MS. This
bervation has several possible implications First igher areas is more similar to most of the corticocortical
onnections than to the thalamic data from MS. This
bservation has several possible implications. First, halamic projections to the higher areas may be more atchy than thalamic projections to the lower areas. halamic projections to the higher areas may be more
atchy than thalamic projections to the lower areas.
cond, epigenetic factors, which may contribute to a high
gree of variability in conticocortical connections atchy than thalamic projections to the lower areas.

lecond, epigenetic factors, which may contribute to a high

legree of variability in corticocortical connections

MacNeil et al. 1997) could play a greater role in shap econd, epigenetic factors, which may contribute to a high egree of variability in corticocortical connections

MacNeil *et al.* 1997), could play a greater role in shaping

the thalamocortical connections of higher-order c The egree of variability in corticocortical connections \bigcup MacNeil *et al.* 1997), could play a greater role in shaping \bigcirc he thalamocortical connections of higher-order cortical \bigcirc reas.

(c) *Interpreting the distribution*

(c) *Interpreting the distribution*
The connections of MS, considered with the near expo-
ntial distributions, that, are observed in some other (c) **Interpreting the distribution**
The connections of MS, considered with the near expo-
ential distributions that are observed in some other
iological systems may provide a clue to the generation The connections of MS, considered with the near exponential distributions that are observed in some other
iological systems, may provide a clue to the generation
of variability in the measurement of neuroanatomical ential distributions that are observed in some other

iological systems, may provide a clue to the generation
 Ω f variability in the measurement of neuroanatomical

miestions Highly variable distributions of the kind provide a clue to the generation
of variability in the measurement of neuroanatomical
rojections. Highly variable distributions of the kind we
have in connection data are commonly found in the observe in the measurement of neuroanatomical rojections. Highly variable distributions of the kind we been the commonly found in the istribution of parasites in populations (Shaw *et al.* 1998) rojections. Highly variable distributions of the kind we
bserve in connection data are commonly found in the
istribution of parasites in populations (Shaw *et al.* 1998;
tear *et al.* 1998). In these cases it can be assume bserve in connection data are commonly found in the istribution of parasites in populations (Shaw *et al.* 1998; tear *et al.* 1998). In these cases, it can be assumed that for ny given individual parasites follow a Poisso istribution of parasites in populations (Shaw *et al.* 1998; tear *et al.* 1998). In these cases, it can be assumed that for ny given individual, parasites follow a Poisson distribu-

tion. If all individuals were the same, this would result in tion. If all individuals were the same, this would result in
a Poisson distribution of parasites across the population.
However, the distribution of parasites appears much more tion. If all individuals were the same, this would result in
a Poisson distribution of parasites across the population.
However, the distribution of parasites appears much more
clumped than the Poisson predicts. This patte a Poisson distribution of parasites across the population.
However, the distribution of parasites appears much more
clumped than the Poisson predicts. This pattern is
obtained because parasites spread between nearby bosts However, the distribution of parasites appears much more
clumped than the Poisson predicts. This pattern is
obtained because parasites spread between nearby hosts,
so that perchabouring animals have similar infection rates clumped than the Poisson predicts. This pattern is
obtained because parasites spread between nearby hosts,
so that neighbouring animals have similar infection rates
(a feature known as 'aggregation') obtained because parasites spread b
so that neighbouring animals have :
(a feature known as 'aggregation').
If instead of a simple Poisson pro If instead of a simple pointing animals have similar infection rates
(a feature known as 'aggregation').
If instead of a simple Poisson process we have a distri-

O ibelling in subsets of afferent neurons with different with very different patterns of extrinsic connections, it is
minar terminations. These factors may be very impor-
ant if the highly variable distribution of connecti is tribution of densities, while larger deposits could yield ments then we would observe a Poisson distribution.

This Alternatively, large tracer deposits that consistently cover

i because the larger deposits could simul bution of Poisson processes with different mean rates, If instead of a simple Poisson process we have a distribution of Poisson processes with different mean rates,
then this can lead to distributions very much like the one
we observe in the connection data. This potentially u bution of Poisson processes with different mean rates,
then this can lead to distributions very much like the one
we observe in the connection data. This potentially unin-
tuitive argument is shown much more simply in figu then this can lead to distributions very much like the one
we observe in the connection data. This potentially unin-
tuitive argument is shown much more simply in figure 7.
Imagine that instead of bost animals we have sing we observe in the connection data. This potentially unintuitive argument is shown much more simply in figure 7.
Imagine that instead of host animals we have single
tracer injections: instead of parasites we have labelled tuitive argument is shown much more simply in figure 7.
Imagine that instead of host animals we have single
tracer injections; instead of parasites we have labelled
cells: and instead of 'aggregation' we have 'blobs' or Imagine that instead of host animals we have single tracer injections; instead of parasites we have labelled cells; and instead of 'aggregation' we have 'blobs' or 'strines' in the cortex (Montero 1981: Symonds $\&$ tracer injections; instead of parasites we have labelled
cells; and instead of 'aggregation' we have 'blobs' or
'stripes' in the cortex (Montero 1981; Symonds & Rosenquist 1984; Sherk 1986; Shipp & Grant 1991). Stripes' in the cortex (Montero 1981; Symonds & Rosenquist 1984; Sherk 1986; Shipp & Grant 1991).
Provided that cortical areas routinely contain patches with very different patterns of extrinsic connections it is Rosenquist 1984; Sherk 1986; Shipp & Grant 1991).
Provided that cortical areas routinely contain patches
with very different patterns of extrinsic connections, it is
straightforward to understand how the distribution of Provided that cortical areas routinely contain patches
with very different patterns of extrinsic connections, it is
straightforward to understand how the distribution of
densities that is observed with small injections (ma with very different patterns of extrinsic connections, it is
straightforward to understand how the distribution of
densities that is observed with small injections (made into
one strine or patch), and assayed with small sa straightforward to understand how the distribution of densities that is observed with small injections (made into one stripe or patch), and assayed with small samples, resembles an exponential If denosits were consistently densities that is observed with small injections (made into
one stripe or patch), and assayed with small samples,
resembles an exponential. If deposits were consistently one stripe or patch), and assayed with small samples,
resembles an exponential. If deposits were consistently
made into the same stripe or patch in different experi-
ments then we would observe a Poisson distribution resembles an exponential. If deposits were consistently
made into the same stripe or patch in different experi-
ments then we would observe a Poisson distribution.
Alternatively large tracer deposits that consistently cove made into the same stripe or patch in different experiments then we would observe a Poisson distribution.
Alternatively, large tracer deposits that consistently cover
an entire 'wavelength' of stripe or patch would generat ments then we would observe a Poisson distribution.
Alternatively, large tracer deposits that consistently cover
an entire 'wavelength' of stripe or patch would generate a
normal distribution of densities These inferences Alternatively, large tracer deposits that consistently cover
an entire 'wavelength' of stripe or patch would generate a
normal distribution of densities. These inferences have an
obvious resonance with observed differences an entire 'wavelength' of stripe or patch would generate a
normal distribution of densities. These inferences have an
obvious resonance with observed differences in variability
in the corticocortical and thalamocortical pr normal distribution of densities. These inferences have an obvious resonance with observed differences in variability
in the corticocortical and thalamocortical projections to
MS cortex obvious resor
in the cortice
MS cortex.

(d) *Measuring the distribution*

A challenging programme of empirical work is needed to put quantitative details on the simple model that we A challenging programme of empirical work is needed
to put quantitative details on the simple model that we
propose to account for variability. Until this is done, it
will be very difficult to interpret within- and interto put quantitative details on the simple model that we
propose to account for variability. Until this is done, it
will be very difficult to interpret within- and inter-
individual differences or differences in the distrib propose to account for variability. Until this is done, it
will be very difficult to interpret within- and inter-
individual differences, or differences in the distributions
of connection densities obtained by injections i will be very difficult to interpret within- and inter-
individual differences, or differences in the distributions
of connection densities obtained by injections in different
areas. First, it is necessary to examine variat individual differences, or differences in the distributions
of connection densities obtained by injections in different
areas. First, it is necessary to examine variations in
connection density with the size and laminar di of connection densities obtained by injections in different
areas. First, it is necessary to examine variations in
connection density with the size and laminar distribution
of tracer denosits, by making two or more denosit areas. First, it is necessary to examine variations in connection density with the size and laminar distribution
of tracer deposits, by making two or more deposits of
distinguishable tracers nearby in the same cortical are connection density with the size and laminar distribution
of tracer deposits, by making two or more deposits of
distinguishable tracers nearby in the same cortical area of
the same individual. Second it will be necessary t of tracer deposits, by making two or more deposits of
distinguishable tracers nearby in the same cortical area of
the same individual. Second, it will be necessary to
determine the natures of within- and inter-individual distinguishable tracers nearby in the same cortical area of
the same individual. Second, it will be necessary to
determine the natures of within- and inter-individual variability. It requires injections of three or more distindetermine the natures of within- and inter-individual variability. It requires injections of three or more distinguishable tracers into the same cortical area of a reason-
able number individuals A minimum of three tracers variability. It requires injections of three or more distinguishable tracers into the same cortical area of a reasonable number individuals. A minimum of three tracers is required to provide information on the shape of the able number individuals. A minimum of three tracers is
required to provide information on the shape of the able number individuals. A minimum of three tracers is
required to provide information on the shape of the
within-individual distribution. It is also necessary to
repeat the procedures in several cortical areas to assess required to provide information on the shape of the
within-individual distribution. It is also necessary to
repeat the procedures in several cortical areas to assess
the variability in the nature of connectivity patterns f within-individual distribution. It is also necessary to
repeat the procedures in several cortical areas to assess
the variability in the nature of connectivity patterns from
one region of cortex to another repeat the procedures in several cortical areas to assess
the variability in the nature of connectivity patterns from
one region of cortex to another.
In conclusion, high variability appears to be a feature the variability in the nature of connectivity patterns from

one region of cortex to another.

In conclusion, high variability appears to be a feature

of all corticocortical and many thalamocortical connec-

tions Variability, presents a challenge for empirical In conclusion, high variability appears to be a feature
of all corticocortical and many thalamocortical connec-
tions. Variability presents a challenge for empirical
neuroanatomy, for attempts to collate and analyse of all corticocortical and many thalamocortical connections. Variability presents a challenge for empirical neuroanatomy, for attempts to collate and analyse connection data and for modelling studies. Connectional tions. Variability presents a challenge for empirical
neuroanatomy, for attempts to collate and analyse
connectionalata, and for modelling studies. Connectional neuroanatomy, for attempts to collate and analyse
connection data, and for modelling studies. Connectional
variability may be important for individual differences in
behaviour and can give us an insight into the local arch connection data, and for modelling studies. Connectional
variability may be important for individual differences in
behaviour, and can give us an insight into the local archi-
tecture of cortical areas. However, given the variability may be important for individual differences in
behaviour, and can give us an insight into the local archi-
tecture of cortical areas. However, given the laborious
nature of quantitative connection tracing it is behaviour, and can give us an insight into the local architecture of cortical areas. However, given the laborious nature of quantitative connection tracing, it is unlikely that variability will be properly addressed without

istological and image-processing methods that allow labelled neurons to be counted automatically.

ibelled neurons to be counted automatically.
This work was supported by the Wellcome Trust (J.W.S.), US
Lational Institute of Neurological Diseases and Stroke and US This work was supported by the Wellcome Trust (J.W.S.), US
[ational Institute of Neurological Diseases and Stroke and US
[ational Institute of Mental Health (B.P.) Thanks to Malcolm his work was supported by the Wellcome Trust (J.W.S.), US
Iational Institute of Neurological Diseases and Stroke and US
Iational Institute of Mental Health (B.P.). Thanks to Malcolm
found and Claus Hilgetag for helpful com Iational Institute of Neurological Diseases and Stroke and US
Iational Institute of Mental Health (B.P.). Thanks to Malcolm
foung and Claus Hilgetag for helpful comments on the nanuscript.

APPENDIX A. PRACTICAL CONSEQUENCES OF A NEAR EXPONENTIAL DISTRIBUTION OF CONNECTION DENSITIES FOR EMPIRICAL NEUROANATOMY

EXPONENTIAL DISTRIBUTION OF CONNECTION
In this appendix, we consider some of the important
neguences of a near exponential distribution of ENSITES FOR EMFINICAL NEUROANATIONT
In this appendix, we consider some of the important
onsequences of a near exponential distribution of
onnection densities for experimental design in connec-In this appendix, we consider some of the important
onsequences of a near exponential distribution of
onnection densities for experimental design in connec-
and neuroanatomy. As the exponential is the most varionsequences of a near exponential distribution of onnection densities for experimental design in connectional neuroanatomy. As the exponential is the most varible possible continuous distribution given non-negative) onal neuroanatomy. As the exponential is the most vari-
ble possible continuous distribution given non-negative
alues, the estimates presented in this section are likely to
percent a relatively pessimistic, yet realistic ble possible continuous distribution given non-negative
alues, the estimates presented in this section are likely to
epresent a relatively pessimistic, yet realistic, picture of
exampling and statistical inference alues, the estimates presented in this section are lil
present a relatively pessimistic, yet realistic, pict
reproblems of sampling and statistical inference.
We provide three practical quides to data that are

present a relatively pessimistic, yet realistic, picture of
e problems of sampling and statistical inference.
We provide three practical guides to data that are expo-
prially distributed. First, it is easy to generate rand ne problems of sampling and statistical inference.
We provide three practical guides to data that are expo-
entially distributed. First, it is easy to generate random
xponentially distributed data from which to calculate We provide three practical guides to data that are exponentially distributed. First, it is easy to generate random xponentially distributed data from which to calculate entially distributed. First, it is easy to generate random
sponentially distributed data from which to calculate
statistics (e.g. mean, median, standard deviation, etc.) and
erform simulations. Numbers from an exponentiall $\frac{1}{2}$ xponentially distributed data from which to calculate $\frac{1}{2}$ catistics (e.g. mean, median, standard deviation, etc.) and erform simulations. Numbers from an exponentially Existics (e.g. mean, median, standard deviation, etc.) and
erform simulations. Numbers from an exponentially
istributed population, x_e , with a mean and standard
eviation of m may be made by generating uniform erform simulations. Numbers from an exponentially
istributed population, x_e , with a mean and standard
eviation of *m* may be made by generating uniform
andom numbers *x* between 0 and 1 and substituting istributed population, x_e , with a mean and standard eviation of m may be made by generating uniform andom numbers, x, between 0 and 1, and substituting are into the following equation (equation (41)) eviation of m may be made by generating uniform andom numbers, x , between 0 and 1, and substituting nem into the following equation (equation (A1)). rem into the following equation (equation (A1)).
 $\lim_{x \to a} e^{-x} = -\mu \ln(x)$. (A1)

ccond, for simple guidance on the relationships between

$$
= -\mu \ln(x). \tag{A1}
$$

 $\epsilon = -\mu \ln(x)$. (A1)
econd, for simple guidance on the relationships between
onfidence intervals bias, and sample size, we provide econd, for simple guidance on the relationships between
onfidence intervals, bias, and sample size, we provide
we graphs (figures 8 and 9). These were produced using econd, for simple guidance on the relationships between
onfidence intervals, bias, and sample size, we provide
wo graphs (figures 8 and 9). These were produced using
quation (3) to generate 10,000 samples in each sample onfidence intervals, bias, and sample size, we provide
wo graphs (figures 8 and 9). These were produced using
quation (3) to generate 10 000 samples in each sample
ze The graphs show the 95% confidence intervals 70% wo graphs (figures 8 and 9). These were produced using
quation (3) to generate 10 000 samples in each sample
ze. The graphs show the 95% confidence intervals, 70%
onfidence intervals (analogous to standard error) quation (3) to generate 10 000 samples in each sample
ze. The graphs show the 95% confidence intervals, 70%
onfidence intervals (analogous to standard error),
redian estimates and bias for the mean (figure 8*a*) and ze. The graphs show the 95% confidence intervals, 70% onfidence intervals (analogous to standard error), redian estimates, and bias for the mean (figure 8*a*) and onfidence intervals (analogous to standard error),
redian estimates, and bias for the mean (figure 8*a*) and
candard deviation (figure 8*b*), for sample sizes ranging
com two to 20 We note that the bias in standard deviaredian estimates, and bias for the mean (figure 8a) and
andard deviation (figure 8b), for sample sizes ranging
- om two to 20. We note that the bias in standard devia-
- on (solid line in figure 8b) is worse for small sam andard deviation (figure $8b$), for sample sizes ranging
om two to 20. We note that the bias in standard devia-
on (solid line in figure $8b$) is worse for small samples.
lso, confidence intervals are asymmetrical unlike The compute intervals are that the bias in standard devia-
on (solid line in figure $8b$) is worse for small samples.
Also, confidence intervals are asymmetrical, unlike the
ormally distributed case. Figure 8 illustrates on (solid line in figure $8b$) is worse for small samples.

Iso, confidence intervals are asymmetrical, unlike the

ormally distributed case. Figure 8 illustrates the fact that

rrors in estimates of connection strengths lso, confidence intervals are asymmetrical, unlike the ormally distributed case. Figure 8 illustrates the fact that rrors in estimates of connection strengths based on small amples can be very large. For example, the 95% confience interval of the mean ranges over a factor of ten

the connuence of estimates of mean (a) and standard dev

then the sample size is five. Estimates of variability

exponential distribution provides a better descriptio amples can be very large. For example, the 95% confi-
ence interval of the mean ranges over a factor of ten
then the sample size is five. Estimates of variability
ased on small samples also show systematic bias ence interval of the mean ranges over a factor

Then the sample size is five. Estimates of variative and samples also show systematic bias.

Third, we provide an indication of the character nen the sample size is five. Estimates of variability
sed on small samples also show systematic bias.
Third, we provide an indication of the chance of
precely identifying differences in the mean values of two

ased on small samples also show systematic bias.

Third, we provide an indication of the chance of

Sorrectly identifying differences in the mean values of two

conventions from which samples of connections are taken population of the chance of
orrectly identifying differences in the mean values of two
populations from which samples of connections are taken.
igure 9 shows the probability that pairs of samples from Figure 9 shows the probability that pairs of samples of two
igure 9 shows the probability that pairs of samples from
any discussion of the probability that pairs of samples from
any discussion of the contract pairs of sam populations from which samples of connections are taken.

igure 9 shows the probability that pairs of samples from

opulations with different mean densities can be correctly

lentified as 'significantly different' at the igure 9 shows the probability that pairs of samples from opulations with different mean densities can be correctly lentified as 'significantly different' at the $p < 0.05$ level. The table was computed by sampling from exp opulations with different mean densities can be correctly
lentified as 'significantly different' at the $p < 0.05$ level.
The table was computed by sampling from exponentially
istributed populations with known mean values dentified as 'significantly different' at the $p < 0.05$ level.
The table was computed by sampling from exponentially istributed populations with known mean values. We The table was computed by sampling from exponentially
istributed populations with known mean values. We
did pairs of samples as 'significantly different' if they
ad completely non-overlapping 85% confidence intervals istributed populations with known mean values. We
dged pairs of samples as 'significantly different' if they
ad completely non-overlapping 85% confidence intervals.
We chose 85% confidence intervals because pairs of dged pairs of samples as 'significantly different' if they ad completely non-overlapping 85% confidence intervals.
We chose 85% confidence intervals, because pairs of annex drawn from exponential populations with the ad completely non-overlapping 85% confidence intervals.
We chose 85% confidence intervals, because pairs of amples drawn from exponential populations with the ame mean have non-overlapping 85% confidence inter-Ve chose 85% confidence intervals, because pairs of amples drawn from exponential populations with the ame mean have non-overlapping 85% confidence interame mean have non-overlapping 85% confidence inter-
als just less than 5% of the time. Therefore, this

Figure 8. Sampling from an exponentially distributed population. The figure provides a guide to sampling bias, and the confidence of estimates of mean (a) and standard deviation population. The figure provides a guide to sampling bias, an
the confidence of estimates of mean (a) and standard deviati
 (b) when sampling from an exponential distribution. The
exponential distribution provides a bette the confidence of estimates of mean (a) and standard devi (b) when sampling from an exponential distribution. The exponential distribution provides a better description of connection data than the normal distribution. Th (b) when sampling from an exponential distribution. T
exponential distribution provides a better description
connection data than the normal distribution. The
relationships are independent of mean connection den exponential distribution provides a better description of
connection data than the normal distribution. The
relationships are independent of mean connection density, so
are expressed as a ratio of the relevant statistic (e connection data than the normal distribution. The
relationships are independent of mean connection density, so
are expressed as a ratio of the relevant statistic (e.g. sample
mean) to the true parameter (e.g. population m relationships are independent of mean connection densi
are expressed as a ratio of the relevant statistic (e.g. same
an) to the true parameter (e.g. population mean).
(e) shows the mean sample mean (solid line) median sam are expressed as a ratio of the relevant statistic (e.g. sample mean) to the true parameter (e.g. population mean).
(*a*) shows the mean sample mean (solid line), median sample mean) to the true parameter (e.g. population mean).

(*a*) shows the mean sample mean (solid line), median sample

mean, 70% confidence intervals (analogous to standard error)

and 95% confidence intervals for a range of (*a*) shows the mean sample mean (solid line), median samp
mean, 70% confidence intervals (analogous to standard err
and 95% confidence intervals for a range of sample sizes.
Sample mean is an unbiased estimate of p mean, 70% confidence intervals (analogous to standard error
and 95% confidence intervals for a range of sample sizes.
Sample mean is an unbiased estimate of population mean
 (x,y) where (x,y) is a realistic of the solid li and 95% confidence intervals for a range of sample sizes.
Sample mean is an unbiased estimate of population mean
(*y*-value of the solid line = 1), but the confidence intervals are wide. (*b*) shows mean sample standard deviation (solid line), (y-value of the solid line = 1), but the confidence intervals are
wide. (b) shows mean sample standard deviation (solid line),
the median sample standard deviation, the 70% confidence
intervals for population standard dev wide. (b) shows mean sample standard deviation (solid line),
the median sample standard deviation, the 70% confidence
intervals for population standard deviation and the 95%
confidence intervals. In contrast to sample me the median sample standard deviation, the 70% confidence
intervals for population standard deviation and the 95%
confidence intervals. In contrast to sample mean, sample
standard deviation is less than one so systematicall intervals for population standard deviation and the 95%
confidence intervals. In contrast to sample mean, sample
standard deviation is less than one, so systematically confidence intervals. In contrast to sample mean, sample
standard deviation is less than one, so systematically
underestimates population standard deviation. This bias is
particularly severe for small sample sizes standard deviation is less than one, so syste
underestimates population standard deviat:
particularly severe for small sample sizes.

BIOLOGICAL CIENCES

ROYA

THE

decided the mean pop. 2 mean pop.
1 igure 9. Statistical power of comparisons between samples
1 and 2 were
1 and 2 were 1 and 2 and 2 The vertical axis shows the igure 9. Statistical power of comparisons between samples
rawn from exponential distributions. Samples 1 and 2 were
rawn from populations 1 and 2. The vertical axis shows the
reportion of pairs of samples in which sample rawn from exponential distributions. Samples 1 and 2 were
rawn from populations 1 and 2. The vertical axis shows the
roportion of pairs of samples in which sample 2 is identified
significantly greater than sample 1 (at b rawn from populations 1 and 2. The vertical axis shows the reportion of pairs of samples in which sample 2 is identified significantly greater than sample 1 (at $p < 0.05$). The repriorible visits shows the ratio of the me roportion of pairs of samples in which sample 2 is identified
s significantly greater than sample 1 (at $p < 0.05$). The
orizontal axis shows the ratio of the means of population 2 s significantly greater than sample 1 (at $p < 0.05$). The

porizontal axis shows the ratio of the means of population 2

nd population 1. A ratio of 1:1 indicates identical population

reaps a ratio of 1:5 indicates a fac perizontal axis shows the ratio of the means of population 2
nd population 1. A ratio of 1:1 indicates identical population
neans, a ratio of 1:5 indicates a factor of five difference in
nulation mean. The curves show the nd population 1. A ratio of 1:1 indicates identical population
neans, a ratio of 1:5 indicates a factor of five difference in
opulation mean. The curves show the relationship between
ratistical power and effect size for s ieans, a ratio of 1:5 indicates a factor of five difference in
opulation mean. The curves show the relationship between
atistical power and effect size for sample sizes of two (dots opulation mean. The curves show the relationship between
atistical power and effect size for sample sizes of two (dots
nd dashes), four (dots), ten (solid line) and 20 (dashes). We
idged pairs of samples as 'significantly in atistical power and effect size for sample sizes of two (dots
nd dashes), four (dots), ten (solid line) and 20 (dashes). We
idged pairs of samples as 'significantly different' if they had
ampletely non-overlapping $85\$ nd dashes), four (dots), ten (solid line) and 20 (dashes). We
idged pairs of samples as 'significantly different' if they had
ompletely non-overlapping 85% confidence intervals. We
hose 85% confidence intervals because idged pairs of samples as 'significantly different' if they has
ompletely non-overlapping 85% confidence intervals. We
hose 85% confidence intervals, because pairs of samples
rawn from exponential populations with the same ompletely non-overlapping 85% confidence intervals. We
hose 85% confidence intervals, because pairs of samples
rawn from exponential populations with the same mean have
on-overlapping 85% confidence intervals just less th hose 85% confidence intervals, because pairs of samples
rawn from exponential populations with the same mean have
on-overlapping 85% confidence intervals just less than 5% of
retime. Therefore, this corresponds to the conv rawn from exponential populations with the same mean have
on-overlapping 85% confidence intervals just less than 5% of
refere. Therefore, this corresponds to the conventionally
coented significance level of a type I error on-overlapping 85% confidence intervals just less than 5% of
re time. Therefore, this corresponds to the conventionally
ccepted significance level of a type I error rate of $p < 0.05$ for
two-tailed test. The figure shows a time. Therefore, this corresponds to the conventionally
ccepted significance level of a type I error rate of $p < 0.05$ for
two-tailed test. The figure shows that for reasonable sample
zee (e.g. ten individuals), connect ccepted significance level of a type I error rate of $p < 0.05$ fo
two-tailed test. The figure shows that for reasonable sample
zes (e.g. ten individuals), connections have to have very
ifferent connection densities to be two-tailed test. The figure shows that for reasonable sample
zes (e.g. ten individuals), connections have to have very
ifferent connection densities to be reliably identified as
gnificantly different. ifferent connection densities to be reliably identified as

CIENCES gnificantly different.
orresponds to the conventionally accepted significance
avel of a type I error rate of $h < 0.05$ for a two-tailed test orresponds to the conventionally accepted significance
evel of a type I error rate of $p < 0.05$ for a two-tailed test. orresponds to the conventionally accepted significance
 $\frac{1}{2}$ vel of a type I error rate of $p < 0.05$ for a two-tailed test.

igure 9 shows that differences in population mean are

erv difficult to reliably detect when vel of a type I error rate of $p < 0.05$ for a two-tailed test.

igure 9 shows that differences in population mean are

ery difficult to reliably detect when sampling from an

xponential distribution. In other words, type igure 9 shows that differences in population mean are
ery difficult to reliably detect when sampling from an
xponential distribution. In other words, type II error
ates tend to be high. Given a sample size of four which is Forthermore, the entire tend to be high. Given a sample size of four, which is a sample size of four, which is the tunusual in connection tracing experiments and a ratio xponential distribution. In other words, type II error
ates tend to be high. Given a sample size of four, which is
ot unusual in connection tracing experiments, and a ratio ates tend to be high. Given a sample size of four, which is
ot unusual in connection tracing experiments, and a ratio
in mean population connection density of 4:1, we would
also get a 'significant' difference around 40% or unusual in connection tracing experiments, and a ratio

in mean population connection density of 4:1, we would

inly get a 'significant' difference around 40% of the time.

It is indicates that typical connection tracin In mean population connection density of 4:1, we would
hy get a 'significant' difference around 40% of the time.
This indicates that typical connection tracing experiments
average experiments only very large differences i may get a 'significant' difference around 40% of the time.

This indicates that typical connection tracing experiments

ay reliably distinguish only very large differences in the

bean density of connections This indicates that typical connection tracing experiments
ay reliably distinguish only very large differences in the
rean density of connections.

REFERENCES

REFERENCES
Casella G. & Berger, R. L. 1990 *Statistical inference*. Belmont,
CA: Wadworth sella G. & Berge
CA: Wadworth.
nerniak C. C. 199 Sasella G. & Berger, R. L. 1990 Statistical inference. Belmont,
CA: Wadworth.
C. C. 1990 The bounded brain: towards quantitative
neuroanatomy $\frac{7}{5}$ Cean Neurosci 2, 58–68

CA: Wadworth.
nerniak, C. C. 1990 The bounded brain: to
neuroanatomy. *J. Cogn. Neurosci*. 2, 58–68.
wwan W. M. Gottlieb D. J. Handrickson. Therniak, C. C. 1990 The bounded brain: towards quantitative
neuroanatomy. J. Cogn. Neurosci. 2, 58–68.
lowan, W. M., Gottlieb, D. I., Hendrickson, A. E., Price, J. L.
 $\frac{k}{2}$. Woolsey T. A. 1972. The autoracliographic d

neuroanatomy. *J. Cogn. Neurosci.* 2, 58–68.
wan, W. M., Gottlieb, D. I., Hendrickson, A. E., Price, J. L.
& Woolsey, T. A. 1972 The autoradiographic demonstration of
axonal connections in the central nervous system. *Brai* wan, W. M., Gottlieb, D. I., Hendrickson, A. E., Price, J. L. & Woolsey, T. A. 1972 The autoradiographic demonstration of [axonal co](http://giorgio.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0006-8993^28^2937L.21[aid=532485,nlm=4110604])nnections in the central nervous system. *Brain Res*.
³⁷ ²¹ –⁵¹ & Woolsey, T. A. 1972 The autoradiographic demonstration of axonal connections in the central nervous system. *Brain Res*. **37**, 21–51.

- De Yeo, E. A. & Van Essen, D. 1985 Segregation of efferent
connections and recentive field properties in visual area V2 of cology E. A. & Van Essen, D. 1985 Segregation of efferent
connections and receptive field properties in visual areaV2 of
the macaque *Nature* 317 58–61 the macaque. *Nature* **317***,* 58-61.
 11 connections and receptive field p
 12 the macaque. *Nature* **317***,* 58–61.
 12 Nature connectionsand receptive field properties in visual area $V2$ of
the macaque. *Nature* 317, 58–61.
Felleman, D. J. & Van Essen, D. C. 1991 Distri[buted hierarchical](http://giorgio.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/1047-3211^28^291L.1[aid=212396,csa=1047-3211^26vol=1^26iss=1^26firstpage=1,nlm=1822724])
processing in the primate cerebral cortex. *Cerebr*, Car
- the macaque. *Nature* 317, 58–61.
Ileman, D. J. & Van Essen, D. C. 1991 Distributed hierarchical
processing in the primate cerebral cortex. *Cerebr. Cortex* 1,
1–47. processing in the primate cerebral cortex. *Cerebr. Cortex* 1, 1–47.
Gerfen, C. R. & Sawchenko, P. E. 1984 An anterograde neuro-
anatomical tracing method that shows the detailed morphology
- 1–47.
erfen, C. R. & Sawchenko, P. E. 1984 An anterograde neuro-
anatomical tracing method that shows the detailed morphology
of neurons their axons, and terminaimmunohistochemicallocaanatomical tracing method that shows the detailed morphology of neurons, their axons, and terminaimmunohistochemicallocaanatomical tracing method that shows the detailed morphology
of neurons, their axons, and terminaimmunohistochemicalloca-
lization of an axonally transported plant lectin, Phaseolus-
vulgarisleukoagglutinin PHA-L *Rrain Re* of neurons, their axons, and terminaimmunohistochemical
lization of an axonally transported plant lectin, Phase
vulgarisleukoagglutinin PHA-L. *Brain Res*. 290, 219–238.
cant S. & Shipp S. 1991 Visuotopic organization of t lizationof an axonally transported plant lectin, Phaseolus-
vulgarisleukoagglutinin PHA-L. *Brain Res*. 290, 219–238.
Grant, S. & Shipp, S. 1991 Visuotopic organization of the lateral
supersylvian area and of an adjacent
- vulgarisleukoagglutinin PHA-L. Brain Res. 290, 219–238.
Grant, S. & Shipp, S. 1991 Visuotopic organization of the lateral
suprasylvian area and of an adjacent area of the ectosylvian rant, S. & Shipp, S. 1991 Visuotopic organization of the lateral suprasylvian area and of an adjacent area of the ectosylvian gyrus of cat cortex—a physiological and connectional study.
Vis Neurosci 6, 315–338 *Suprasylvian area and of*
Vis. Neurosci. **6**, 315–338.
Vis. Neurosci. **6**, 315–338. gyrusof cat cortex—a physiological and connectional study.
Vis. Neurosci. 6, 315–338.
Kristensson, K., Olsson, Y. & Sjostrand, J. 1971 Axonal uptake
and retrograde transport of exogenous proteins in the bypo-
- Vis. Neurosci. 6, 315–338.
cistensson, K., Olsson, Y. & Sjostrand, J. 1971 Axonal uptake
and retrograde transport of exogenous proteins in the hypo-
glossal nerve, Brain Res. 32, 399–406. and retrograde transport of exogenous proteins in the hypo-
glossal nerve. *Brain Res.* **32**, 399-406. andretrograde transport of exogenous proteins in the hypoglossal nerve. *Brain Res.* 32, 399–406.
Le Gros Clark, W. E. 1932 The structure and connections of the the structure R_{train} 55, 406–470
- glossal nerve. *Brain Res.* **32**, 399:
 *Gros Clark, W. E. 1932 The st

thalamus. <i>Brain* **55**, 406–470.
 Gros Clark W. E. 1942 The Le Gros Clark, W. E. 1932 The structure and connections of the thalamus. *Brain* 55, 406–470.
Le Gros Clark, W. E. 1942 The visual centres of the brain and their connections P_{bus} P_{ev} 22 905–939
- thalamus. *Brain* 55, 406–470.
Le Gros Clark, W. E. 1942 The visual centres of the brain and
their connections. *Phys. Rev.* **22**, 205–232.
- MacNeil, M. A., Lomber, S. G. & Payne, B. R. 1997 Thalamic their connections. *Phys. Rev.* 22, 205–232.
acNeil, M. A., Lomber, S. G. & Payne, B. R. 1997 Thalamic
and cortical projections to the middle suprasylvian cortex of
cats: constancy and variation. *Expl. Regin. Res*. 114, acNeil, M. A., Lomber, S. G. & Payne, B. R. 1997 Thalar
and cortical projections to the middle suprasylvian cortex
cats: constancy and variation. *Expl Brain. Res.* **114**, 24–32.
archi V. & Algeri. G. 1895 Sulle degenerazi andcortical projections to the middle suprasylvian cortex of
cats: constancy and variation. *Expl Brain. Res.* **114**, 24–32.
Marchi, V. & Algeri, G. 1895 Sulle degenerazioni discendenti
consecutive a lesioni della cortec
- cats: constancy and variation. *Expl Brain. Res.* **114**, 24–32.
Marchi, V. & Algeri, G. 1895 Sulle degenerazioni discendenti consecutive a lesioni della corteccia cerebrale. *Nota Pre. Riv. Sper. Di Freniat.* **11**, 429. consecutive a lesioni della corteccia cerebrale. Nota Pre. Riv. consecutive a lesioni della corteccia cerebrale. *Nota Pre. Riv.*
Sper. Di Freniat. 11, 429.
Meynert, T. 1890 Über das Zusammenwirken der Gerhirntheile.
Verhandlungen des X. Internat. Mediz. Kongress. Berlin 1. 173–190.
- *Sper. Di Freniat.* **11**, 429.
eynert, T. 1890 Über das Zusammenwirken der Gerhirntheile.
Verhandlungen des X. Internat. Mediz. Kongress. Berlin **1**, 173–190.
ontero V. M. 1981 Topography of cortico-cortical connections Meynert, T. 1890 Über das Zusammenwirken der Gerhirntheile.
 Verhandlungen des X. Internat. Mediz. Kongress. Berlin **1**, 173–190.

Montero, V. M. 1981 Topography of cortico-cortical connections

from the stripte cortex i
- *Verhandlungen des X. Internat. Mediz. Kongress. Berlin* **1**, 173–190.

ontero, V. M. 1981 Topography of cortico-cortical connections

from the striate cortex in the cat. *Brain Behav. Evol.* **18**, 194–218.

usil S. V. & O Montero,V. M. 1981 Topography of cortico-cortical connections
from the striate cortex in the cat. *Brain Behav. Evol*. **18**, 194–218.
Musil, S. Y. & Olson, C. R. 1988*a* Organization of the cortical
and subcortical projec
- from the striate cortex in the cat. *Brain Behav. Evol.* **18**, 194–218.
usil, S. Y. & Olson, C. R. 1988*a* Organization of the cortical
and su[bcortical projections to the me](http://giorgio.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0021-9967^28^29272L.219[aid=532491,csa=0021-9967^26vol=272^26iss=2^26firstpage=219,nlm=2456312])dial prefrontal cortex in
the cat. 7 Camb. Neura and subcortical projections to the medial prefrontal cortex in the cat. *J. Comp. Neurol.* 272, 219-241.
- Musil, S. Y. & Olson, C. R. 1988*^b* Organization of the cortical the cat. *J. Comp. Neurol.* 272, 219–241.
usil, S. Y. & Olson, C. R. 1988b Organization of the cortical
and subcortical projections to the anterior cingulate cortex in
the cat. *J. Comp. Neurol.* 272, 203–218. usil, S. Y. & Olson, C. R. 1988b Organ
and subcortical projections to the anter
the cat. *J. Comp. Neurol.* 272, 203–218.
usil S. V. & Olson, C. R. 1991 Cortic andsubcortical projections to the anterior cingulate cortex in
the cat. $\tilde{\jmath}$. Comp. Neurol. 272, 203–218.
Musil, S. Y. & Olson, C. R. 1991 Cortical areas in the medial
frontal-lobe of the cat delineated by quantitat
- the cat. *J. Comp. Neurol.* **272**, 203–218.
usil, S. Y. & Olson, C. R. 1991 Cortical areas in the medial
frontal-lobe of the cat delineated by quantitative-analysis of
thelamic afferents *J. Comb. Neurol* **308** 457–466. usil, S. Y. & Olson, C. R. 1991 Cortical areas in
frontal-lobe of the cat delineated by quantitative-
thalamic afferents. *J. Comp. Neurol.* **308**, 457–466. frontal-lobeof the cat delineated by quantitative-analysis of
thalamic afferents. J. Comp. Neurol. **308**, 457–466.
Nauta, W. J. H. & Gygax, P. A. 1954 Silver impregnation for
degenerating ayons in the central nervous sys
- thalamic afferents. *J. Comp. Neurol.* **308**, 457–466.

uuta, W. J. H. & Gygax, P. A. 1954 Silver impregnation for

degenerating axons in the central nervous system: a modified

technique *Stain Technol* **20** 91–93 uta, W. J. H. & Gygax, P. A. 195
degenerating axons in the central n
technique. *Stain Technol*. **29**, 91–93.
son. C. R. & Musil. S. V. 1992. To: degenerating axons in the central nervous system: a modified
technique. *Stain Technol*. **29**, 91–93.
Olson, C. R. & Musil, S. Y. 1992 Topographic organization of
cortical and subcortical projections to posterior cinculate
- technique. *Stain Technol.* **29**, 91–93.
son, C. R. & Musil, S. Y. 1992 Topographic organization of
cortical and subcortical projections to posterior cingulate
cortex in the cat—evidence for somatic ocular and complex son, C. R. & Musil, S. Y. 1992 Topographic organization of cortical and subcortical projections to posterior cingulate cortex in the cat—evidence for somatic, ocular, and complex subregions $\frac{7 \text{ } Camb\; Neural\ 324\ 237-260}$ cortical and subcortical projections to posterior cingulate cortex in the cat—evidence for somatic, ocular, and complex subregions. $\tilde{\jmath}$. *Comp. Neurol.* **324**, 237-260. cortexin the cat—evidence for somatic, ocular, and complex
subregions. J. Comp. Neurol. **324**, 237–260.
Pandya, D. N. & Yeterian, E. H. 1985 Architecture and connec-
tions. of cortical association areas. In *Cerebral cate*
- subregions. J. Comp. Neurol. **324**, 237–260.
ndya, D. N. & Yeterian, E. H. 1985 Architecture and connections of cortical association areas. In *Cerebral cortex*. 4.
Association and auditory certices (ed. A. Peters & E. G. ndya, D. N. & Yeterian, E. H. 1985 Architecture and connections of cortical association areas. In *Cerebral cortex*. 4.
Association and auditory cortices (ed. A. Peters & E. G. Jones),
pp. 1–61 New York and London: Plenu tions of cortical association areas. In *Cereb:*
Association and auditory cortices (ed. A. Peters &
pp. 1–61. New York and London: Plenum Press.
yne B. R. Connors C. & Cornwell P. 1991 Survi Association and auditory cortices (ed. A. Peters & E. G. Jones),
pp. 1–61. New York and London: Plenum Press.
Payne, B. R., Connors, C. & Cornwell, P. 1991 Survival and death
of neurons in cortical area PMI S after removal
- pp. 1–61. New York and London: Plenum Press.
yne, B. R., Connors, C. & Cornwell, P. 1991 Survival and death
of neurons in cortical area PMLS after removal or areas 17, 18,
and 19 from cats and kittens *Cerebr Cortex* 1, 46 yne, B. R., Connors, C. & Cornwell, P. 1991 Survival and 19 from cats and kittens. *Cerebr. Cortex* **1**, 469–491.

and 19 from cats and kittens. *Cerebr. Cortex* **1**, 469–491. %of neurons in cortical area PMLS after removal or areas 17, 18,
and 19 from cats and kittens. *Cerebr. Cortex* 1, 469–491.
Polyak, S. 1927 An experimental study on the association,
callosal and projection fibres of the
- and 19 from cats and kittens. *Cerebr. Cortex* **1**, 469–491.
lyak, S. 1927 An experimental study on the association,
callosal, and projection fibres of the cerebral cortex of the cat.
J. Comp. Neurol. **44**, 197–254.
lyak rellosal, and projection fibres of the cerebral cortex of the cat.
 J. Comp. Neurol. **44**, 197–254.

Polyak, S. 1933 *The main afferent fiber systems in the cerebral cortex of*
 termates Berkeley CA: University of Cali
- *J. Comp. Neurol.* **44**, 197–254.
lyak, S. 1933 *The main afferent fiber systems in the cerebral cortex of*
primates. Berkeley, CA: University of California Publ. Anat.
vol. 2 primates. Berkeley, CA: University of California Publ. Anat. vol. 2. primates. Berkeley, CA: University of California Publ. Anat.
vol. 2.
Raczkowski, D. & Rosenquist, A. C. 1983 Connections of the
multiple visual cortical areas with the lateral posterior.
- vol. 2.
iczkowski, D. & Rosenquist, A. C. 1983 Connections of the
multiple visual cortical areas with the lateral posterior-
pulyinar complex and adjacent thalamic puclei in the cat. 7 nczkowski, D. & Rosenquist, A. C. 1983 Connections of the multiple visual cortical areas with the lateral posterior-
pulvinar complex and adjacent thalamic nuclei in the cat. *J.*
Neurosci 3 1919–1949 multiple visual cortical areas with the lateral posterior-
pulvinar complex and adjacent thalamic nuclei in the cat. \tilde{J} .
Neurosci. 3, 1912–1942.
Rose, J. E. & Woolsey, C. N. 1948 Structure and relations of pulvinarcomplex and adjacent thalamic nuclei in the cat. \tilde{J} .
- *Neurosci.* **3**, 1912–1942.
see, J. E. & Woolsey, C. N. 1948 Structure and relations of
limbic cortex and anterior thalamic nuclei in rabbit and cat.
7 Cemp. Neural **80**, 270–438. *J. E. & Woolsey, C. N. 1*
J. Comp. Neurol. **89**, 279–438.

THE ROYA

PHILOSOPHICAL
TRANSACTIONS

BIOLOGICAL

 $\overline{\alpha}$

HL

Scannell, J. W. 1997 Determining cortical landscapes. *Nature*
386–452 annell, J. ¹
386, 452.
annell I W cannell,J. W. 1997 Determining cortical landscapes. *Nature*
386, 452.
cannell, J. W., Blakemore, C. & Young, M. P 1995 Analysis of
connectivity in the cat cerebral cortex 7 *Neurosci* 15, 1463–1483

386, 452.
annell, J. W., Blakemore, C. & Young, M. P 1995 Analysis of
connectivity in the cat cerebral cortex. *J. Neurosci*. **15**, 1463–1483.
aw, D. J. Grenfell, B. T. & Dobson, A. P. 1998. Patterns of cannell,J. W., Blakemore, C. & Young, M. P 1995 Analysis of
connectivity in the cat cerebral cortex. J. Neurosci. 15, 1463–1483.
haw, D. J., Grenfell, B. T. & Dobson, A. P. 1998 Patterns of
macronarysite aggregation in wi

connectivity in the cat cerebral cortex. *J. Neurosci*. **15**, 1463–1483.
aw, D. J., Grenfell, B. T. & Dobson, A. P. 1998 Patterns of
macroparasite aggregation in wildlife host populations.
Parasitology **117**, 597–610 haw, D. J., Grenfell, B. T. & Dobson, A. P. 1998 Patterns of macroparasite aggregation in wildlife host populations.
Parasitology **117**, 597-610.

herk,H. 1986 Coincidence of patchy inputs from the lateral *Parasitology* 117, 597–610.
erk, H. 1986 Coincidence of patchy inputs from the lateral
geniculate complex and area 17 to the cat's Clare–Bishop
area 7 Camb Neural 253 105–120 erk, H. 1986 Coincidence of patchy
geniculate complex and area 17 to
area. *J. Comp. Neurol.* **253**, 105–120.
erk H. & Ombrellaro M. 1988 Th geniculatecomplex and area 17 to the cat's Clare–Bishop
area. \tilde{J} . Comp. Neurol. 253, 105–120.
herk, H. & Ombrellaro, M. 1988 The retinogeniculate match
between area 17 and its targets in visual suprasylvian cortex

area. *J. Comp. Neurol.* **253**, 105–120.
erk, H. & Ombrellaro, M. 1988 The retinogeniculate match
between area 17 and its targets in visual suprasylvian cortex.
Expl Brain Res **72** 225–236 erk, H. & Ombrellaro, M. 19

between area 17 and its targe
 Expl Brain Res. **72**, 225–236.

ipp S. & Grant S. 1991 Ore

ExplBrain Res. 72, 225–236.
hipp, S. & Grant, S. 1991 Organization of reciprocal connec-Expl Brain Res. 72, 225–236.
ipp, S. & Grant, S. 1991 Organization of reciprocal connections beteen area 17 and the lateral suprasylvian area of cat
visual cortex *Vis. Neurosci* 6, 339–355. visual cortex. *Vis. Neurosci*. **6**, 339–355.
olomon, D. L. 1983 The spatial distribution tionsbeteen area 17 and the lateral suprasylvian area of cat

visual cortex. Vis. Neurosci. 6, 339–355.

olomon, D. L. 1983 The spatial distribution of

cabbage butterfly eggs. Life science models, yol. 4 (ed. H

cabbage butter£y eggs. *Life science models*, vol. 4 (ed. H.

Marcus-Roberts & M. Thompson), pp. 350-366. New York: Springer.

- Stear, M. J., Bairden, K., Bishop S. C., Gettinby, G., Springer.
ear, M. J., Bairden, K., Bishop S. C., Gettinby, G.,
McKellar, Q. A., Park, M., Strain, S. & Wallace, D. S. 1998
The processes influencing the distribution of parasitic nemaear, M. J., Bairden, K., Bishop S. C., Gettinby, G., McKellar, Q. A., Park, M., Strain, S. & Wallace, D. S. 1998
The processes influencing the distribution of parasitic nema-
todes among naturally infected lambs. *Parasite* The processes influencing the distribution of parasitic nematodes among naturally infected lambs. *Parasitology* 117, 165–171. todes among naturally infected lambs. *Parasitology* 117, 165–171.
Symonds, L. L. & Rosenquist, A. C. 1984 Corticocortical connections among visual areas in the cat. 7 *Comb* Neural
- 165–171.
monds, L. L. & Rosenquist, A. C. 1984 Corticocortical
connections among visual areas in the cat. *[J. Comp. Neurol.](http://giorgio.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0021-9967^28^29229L.1[aid=532475,csa=0021-9967^26vol=229^26iss=1^26firstpage=1,nlm=6490972])*
229 1–38 monds, L.
connections
229, 1–38.
ung. M. connectionsamong visual areas in the cat. \tilde{J} . Comp. Neurol.
229, 1–38.
Young, M. P. 1993 The organi[zation of neural systems](http://giorgio.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0962-8452^28^29252L.13[aid=532430,csa=0962-8452^26vol=252^26iss=1333^26firstpage=13,nlm=8389046])
in the primate cerebral cortex *Proc. R. Sec. Land* R.252.
- in the primate cerebral cortex. *Proc. R. Soc. Lond.* ^B **²⁵²**, 13^18. inthe primate cerebral cortex. *Proc. R. Soc. Lond.* B 252, 13-18.
Zeki, S. & Shipp, S. 1988 The functional logic of cortical connections $Nature$ 335 311-317
- 13–18.
ki, S. & Shipp, S. 1988 The f
connections. *Nature* **335**, 311–317.
ki, S. & Shipp, S. 1989 Modular. Zeki, S. & Shipp, S. 1988 The functional logic of cortical connections. *Nature* **335**, 311-317.
Zeki, S. & Shipp, S. 1989 Modular connections between areas V.2 and V.4 of macague monkey visual cortex. *Fur* 7. *Naurosci*
- connections. *Nature* **335**, 311–317.

ki, S. & Shipp, S. 1989 Modular connections between areas

V2 and V4 of macaque monkey visual cortex. *Eur. J. Neurosci*.
 1 494–506 V₂ and V₄ of macaque monkey visual cortex. *Eur. J. Neurosci*.
1, 494–506.