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THE ROYAL SOCIETY

Coordinate-independent mapping of structural and functional data by objective relational transformation (ORT)

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Neuroscience has produced an enormous amount of structural and functional data. Powerful database systems are required to make these data accessible for computational approaches such as higher-order analyses and simulations. Available databases for key data such as anatomical and functional connectivity between cortical areas, however, are still hampered by methodological problems. These problems arise predominantly from the parcellation problem, the use of incongruent parcellation schemes by different authors. We here present a coordinate-independent mathematical method to overcome this problem: objective relational transformation (ORT). Based on new classifications for brain data and on methods from theoretical computer science, ORT represents a formally defined, transparent transformation method for reproducible, coordinate-independent mapping of brain data to freely chosen parcellation schemes. We describe the methodology of ORT and discuss its strengths and limitations. Using two practical examples, we show that ORT in conjunction with connectivity databases like CoCoMac (http://www.cocomac.org) is an important tool for analyses of cortical organization and structure–function relationships.

Keywords: mapping method; analysis; database; cortex; connectivity; structure–function relationship

1. INTRODUCTION

Throughout the past few decades the different fields of neuroscience have accumulated an enormous amount of data from the subcellular to the systems level. Paradoxically, this successful work has turned into a serious problem: the explosive growth of new information creates increasing problems in the integration of the available data into comprehensive models of structure–function relationships in the brain (Huerta *et al.* 1993). This difficulty is the more severe, the higher the brain level analysed and the more modalities of brain data involved, and is clearly evident when studying the structural organization and computational principles of the cerebral cortex (Burns & Young, this issue; Felleman & Van Essen 1991; Hilgetag *et al.* 1996; Hilgetag, Burns, O'Neill, Scannell & Young, this issue; Scannell *et al.* 1995; Young 1992, 1993; Young *et al.* 1995). Analytical approaches to these questions cannot be framed on the basis of individual experiments and require databases that integrate the huge numbers of experimental findings for the various modalities of brain data, such as connectivity between distinct brain structures; electrophysiological data, both of single neurons and networks; receptor distribution data; and morphological data on different neuron types (Huerta *et al.* 1993). In other disciplines, databases and other techniques of computer-based information management have already become indispensable tools for scientific progress. For example, the impressive development of genetics and molecular biology would have been impossible without databases of gene sequences and protein structures (Frishman *et al.* 1998). A new and increasingly important discipline, in which novel insights and experimentally testable predictions are inferred from mathematical analyses of these data, has emerged. It is called 'bioinformatics'.

The corresponding approach in neuroscience—neuroinformatics—is much less acknowledged. The most notable developments in neuroinformatics have concerned databases representing data on structural connectivity (Burns 1997; Felleman & Van Essen 1991; Scannell *et al.* 1995; Young 1993). The motivation for these databases is the key role that data on association fibre connectivity play in unravelling the organization of the cerebral cortex. A large number of tracer studies have been performed during the last several decades to unravel the connections between cortical areas and subsets of these data have been collated in the studies above. Representing the lines of communication between the various cortical areas, the complex wiring patterns between areas cannot be inferred by intuition alone and so this approach appears to be a necessary first step towards understanding the organization of brain networks.

Unfortunately, integration and comparison of the results of experimental studies has always been difficult due to the incompatibility of the many parcellation schemes used by experimenters. First, a variety of different criteria have been employed by past and present investigators to parcel the cerebral cortex into structural and/or functional units (for reviews, see Van Essen 1985;

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Zilles 1990). Moreover, most of the criteria used for parcellation (e.g. cytoarchitectonics, myeloarchitectonics, enzyme staining) are not observer-independent, but yield different results among different authors. Few attempts have been made to develop and apply more observer-independent methods (e.g. Schleicher *et al.* 1999; Schleicher & Zilles 1990) or to define operationalized criteria for the delineation of areal boundaries (e.g. Carmichael & Price 1994). As a result of these methodological ambiguities different maps often differ considerably in areal boundaries. Nevertheless, the same name has sometimes been given to areas that are only partially coextensive. An example of this occurrence is the supplementary motor area (SMA), which refers to several medial premotor areas all designated as SMA but with different extents and locations (Wise *et al.* 1996).

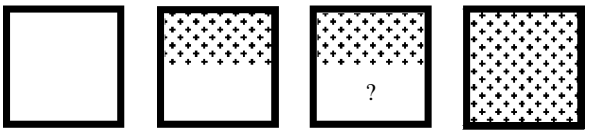
Such confusion is highly problematic for the construction of integrative databases: How can the data of different authors using different maps be made comparable to each other? A desirable solution might be spatial mapping of experimental data on to a spatial reference system or reference brain. Such a technique based on nonlinear transformations of high-resolution MRI images is currently being developed (Roland & Zilles 1994, 1996). However, this promising approach will only be applicable to future experiments and not to the large number of already performed and published experiments, for which no coordinates are given and no standard references have been established. Therefore, all available connectivity databases and data collations (Burns 1997; Felleman & Van Essen 1991; Scannell *et al.* 1995; Young 1993) had to adopt a pragmatic method to make use of the published data. An *a priori* 'reference map' was defined to which all the published findings were mapped, according to the judgement and individual criteria of the respective database collator. These judgements concerned assumptions about the relations between the reference map and all other maps, rules on how to deal with contradictory findings, and so on. The areal relations for mapping published data to the reference map essentially had three different origins: (i) they resulted from self-conducted comparisons of maps on topological grounds (e.g. relative position of areas, relation of areas to morphological landmarks such as sulci); (ii) they were based on opinions on these matters published by other authors; or (iii) they referred to experimental investigations specifically designed to investigate the validity of a given parcellation scheme (e.g. Geyer *et al.* 1996). Spatial mapping of published data not being available, there is little choice other than to use such criteria for the conversion of data between different brain maps. However, areal relations and other criteria underlying the transformation should be explicitly represented by the database, otherwise the transformation process to the reference map remains opaque for anyone except the database constructor. For example, Felleman & Van Essen (1991) and Scannell *et al.* (1995) tabulated alternative schemes for areas of their maps, but did not indicate clearly what relationships were used for the transformations between maps. Furthermore, the existing databases contain only transformed data, so that it is difficult to reconstruct the original data without returning to the primary reports. Finally, existing databases do not allow an interrogator to extract data into any user-defined parcellation scheme, but restrict the format of data output to their reference map.

In spite of these problems, the existing databases represent important progress in neuroscience, as they are the first systematic attempts to integrate the huge amount of published connectivity data. The important insights gained by analytical studies in recent years (e.g. Hilgetag *et al.* 1996; Hilgetag, Burns, O'Neill, Scannell & Young, this issue; Kötter & Sommer, this issue; Young 1992) into cortical and thalamocortical organization and systems-level structure–function relationships would have been impossible without them. Also, the development of the methodology described here benefited considerably from the experiences gained with the previous database systems. However, to overcome the remaining methodological problems, we have formulated some general conditions that a methodology for databases of neuroanatomical data system should meet.

(i) Objectivity: each data entry should be represented in its original nomenclature and should be clearly referenced.
(ii) Reproducibility: the mapping process should be performed by clearly defined algorithms to ensure identical results for repeated transformations of the same data and relations.
(iii) Transparency: all criteria of the mapping procedure should be fully documented. Also, all available opinions of different authors (both conflicting and confirming) on relationships between maps should be represented.
(iv) Flexibility: the data should be convertible to a freely chosen target map.
(v) Simplicity: the method should be easily applicable to already published data.

Based on these five criteria, we have developed a mathematical methodology for the conversion of brain data between different parcellation schemes: objective relational transformation (ORT). In essence, ORT relies on (i) general classifications for brain data and for the logical relations between cortical areas from different maps; (ii) a set of transformation rules which operate on these classifications for the conversion of brain data between different cortical maps; and (iii) graph-theoretical algorithms and finite automata for optimization of data conversion. ORTenables databases to store brain data in their original parcellation scheme and to convert the data from incongruent maps objectively and reproducibly into any user-chosen cortical parcellation scheme. In this way, data from different sources can be integrated and made available for all kinds of studies, e.g. analyses of cortical organization and structure–function relationships (e.g. Hilgetag *et al.* 1997; Stephan *et al.*, this issue) as well as modelling approaches.

In this paper, we present the various components of ORT first by an informal general description, followed by an explicit mathematical definition. The reader who is mainly interested in the principles of ORT can thus skip the more formal parts. Some mathematical descriptions, which are important for correct implementation of ORT-based algorithms in databases but not central to the understanding of the methodology, are described in Appendix A. Whereas accounts of basic features of ORT



igure 1. Extension codes (ECs) for the classification of brain ata according to the extent that their information is valid for given cortical area. *N*, the information is valid for no part of ne area. *P*, the information is partially valid for the area. *X*, the information exists, i.e. it is valid at least for a part of ne area, maybe even for its complete extent. *C*, the informaon is valid for the complete extent of the area.

ave been published before (Stephan & Kötter 1998, 999), this article is the first complete description of this ethodology.

2. METHODS

(a) *New classifications for brain data: extension and relation codes*

The first step of developing a formal method for converting rain data between different parcellation schemes is to define oth what information is needed for this process and how it can e classified and represented. Furthermore, the chosen classificaons should apply to published data as easily and universally as ossible. We here present two such classifications: one for the nformation referring to a cortical area (extension codes) and ne for the logical relation between areas of different brain aps (relation codes).

Any single neuroanatomical or neurophysiological datum on ne cerebral cortex can be understood as information being alid for a restricted part of the cortex. For example, injecting racer substance into any given part of the cortex will label some reas whereas others will remain unlabelled. But even within ne specific area, this information can be further specified. For xample, an area labelled by tracer substance may be ompletely labelled, it may be only partially labelled or just the xistence of label but not its extent may be known.

Based on these considerations, one can classify brain data ccording to the extent to which their information is valid for a pecific cortical area *A*. We call this classification the extension odes (ECs) and distinguish five cases (figure 1):

(i) EC $(A) = N$: the information is valid for no part of A.
(ii) EC $(A) = P$: the information is valid partially for A, i.e. there are subparts for which it is not valid.
iii) EC $(A) = C$: the information is valid for the complete extent of A, i.e. for every subpart of A.
iv) EC $(A) = X$: the information exists for A, i.e. due to lack of precise information it is valid at least for a part of A, maybe even for its complete extent.
(v) EC $(A) = U$: it is unknown whether and to what extent the information is valid for A.

n the following mathematical descriptions, the set C_{EC} is efined to contain these five ECs, i.e. $C_{EC} = \{N, P, X, C, U\}$.

It should be noted that this classification is independent of ne actual modality of the brain datum, i.e. it can be used to escribe both structural (e.g. labelled neurons, transmitter, nzyme or receptor distributions) and functional data (e.g. atterns of activated cortical areas at a given point of time). The ctual application of the ECs, however, varies depending on whether one treats cortical areas as three-dimensional or idealized two-dimensional objects. Although ECs are principally applicable in both cases, the second option that abstracts from the spatial laminar locations of, for example, labelled neurons within an area and instead describes the extent of the information after projection on to a two-dimensional plane (see figure 1), usually is more appropriate for cortical data. The simple reason for this is that a large proportion of the available data in the literature predominantly provides two-dimensional information, for example by surface views on labelled areas in tracer studies.

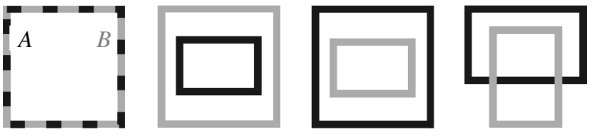


Figure 2. Relation codes (RCs) for the classification of relations between cortical areas from different maps. RC$(A, B) = I$: A and B have identical boundaries. RC$(A, B) = S$: A is a sub-area of B. RC$(A, B) = L$: A is a larger area than B, i.e. A includes B. RC$(A, B) = O$: A and B overlap, i.e. they are partially coextensive.

One of the consequences of inter-individual variability of brain shape and folding is that comparing two different parcellation schemes means to implicitly assume a 'standard' or 'reference cortex' on which the two maps are simultaneously projected. Various authors have compared different parcellation schemes (e.g. von Bonin & Bailey 1947; Felleman & Van Essen 1991; Preuss & Goldman-Rakic 1991*a*,*b*), but no formal classification for the relation of two areas A and B in two different maps A' and B' has been presented so far. We therefore developed the following classification of relation codes (RCs), which covers all possible logical relations that such areas A and B can possibly have on a standard cortex (figure 2).

(i) RC $(A, B) = I$: A and B have identical boundaries.
(ii) RC $(A, B) = S$: A is a sub-area of B, i.e. A is contained by B.
(iii) RC $(A, B) = L$: A is larger than B, i.e. A contains B.
(iv) RC $(A, B) = O$: A and B overlap, i.e. A covers some parts of the standard cortex which is not covered by B and vice versa.
(v) RC $(A, B) = D$: A and B are disjoint, i.e. A and B are not coextensive on the standard cortex in any way.

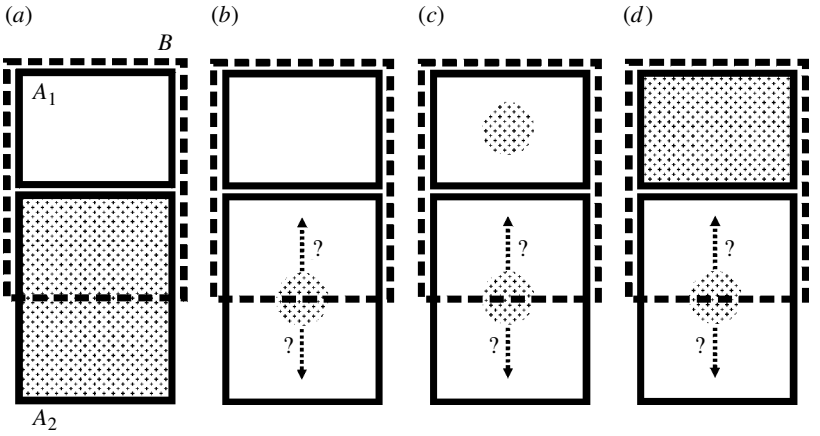
In the following mathematical descriptions, the set C_{RC} is defined to contain the four non-disjoint RCs, i.e. $C_{RC} = \{I, S, L, O\}$.

(b) *The algebra of transformation (AT)*

Based on the two sets C_{EC} and C_{RC}, we can now formulate simple rules as small building blocks of a general answer to our initial question: How can we transform a specific piece of information (i.e. one or several ECs) from one map to another, given that we know about the relations (RCs) of the involved areas of both maps?

If we look at some simple situations, we can see the result immediately—or we see that there is no unequivocal result at all. Figure 3 shows four such simple examples: we here deal with two areas A_1 and A_2 of a source map A' and an area B of a target map B' with A_1 being a sub-area of B (i.e. RC$(A_1, B) = S$) and A_2 overlapping with B (i.e. RC$(A_2, B) = O$).

If A_1 contains no information (EC$(A_1) = N$) whereas A_2 contains complete information (EC$(A_2) = C$), then transformation to area B in the target map B' results in EC$(B) = P$



igure 3. Four examples of simple EC–RC constellations. For all examples $RC(A_1, B) = S$, $RC(A_2, B) = O$. (*a*) $EC(A_1) = N$, $C(A_2) = C$, resulting $EC(B) = P$. (*b*) $EC(A_1) = N$, $EC(A_2) = P$, resulting $EC(B) = U$. (*c*) $EC(A_1) = P$, $EC(A_2) = P$, resulting $C(B) = P$. (*d*) $EC(A_1) = C$, $EC(A_2) = P$, resulting $EC(B) = X$.

igure 3*a*). If, however, A_2 only carries partial information $EC(A_2) = P$), then we cannot decide unambiguously: depending n the exact spatial location of the information (which we do ot know), the result for area B might either be $EC(B) = P$ or $C(B) = N$ (figure 3*b*). This ambiguity is resolved, however, if $_1$ carries partial information ($EC(A_1) = P$) as well (figure 3*c*). hen the information of A_2 no longer matters (as we will see ter, partial information of a sub-area dominates over any other nformation). It does matter though, if the information ontained by A_1 is not partial, but complete ($EC(A_1) = C$). Then he spatial location and the extent of the information contained y A_2 decides whether $EC(B) = P$ or $EC(B) = C$. As we are ertain about the validity of the information for B but cannot etermine the extent to which it is valid, this situation is consis- ent with the above definition of the existing EC, i.e. $EC(B) = X$ igure 3*d*).

Constellations can become much more complex than these mple examples, though. Furthermore, the amount of data ored by databases is far too large for manual handling and equires automatic, observer-independent processing. Therefore, e have to make the parcellation problem accessible for an algo- thmic approach. In other words, we need a formal description r a set of general transformation rules operating on our two ets C_{EC} and C_{RC}. In computer science, such a construction of everal sets and operations is called a 'heterogeneous algebra' Güting 1992). In the following, we will therefore refer to this set f rules as the 'algebra of transformation' or simply AT.

For sub- and overlapping areas, the general principle of our T is as follows: imagine we intend to convert information bout an area A from map A' to map B'. First, we have to find ll areas $B_1, \ldots, B_m$ ($m \geqslant 1$) in map B' that are coextensive in me way with area A on standard cortex and thus are the rget areas of the mapping process. Then, for each area B_k $\leqslant k \leqslant m$), we have to determine all areas $A_1, \ldots, A_n$ ($n \geqslant 1$) in ap A' which, together with A, are coextensive in some way ith area B_k. We decide step-by-step how the information of ach of the areas $A_1, \ldots, A_n$ is converted to area B_k. At each ep we first consider what we know about the information of B_k far. We call this result of previous transformations $EC_{prev}(B_k)$. hen we turn to the currently processed area A_i ($1 \leqslant i \leqslant n$) of ap A', determine its relation to B_k (i.e. $RC(A_i, B_k)$) and its nformation (i.e. $EC(A_i)$) and use the appropriate rule (see table) for the triplet ($EC_{prev}(B_k)$, $RC(A_i, B_k)$, $EC(A_i)$). The trans- rmation rule delivers a temporarily resulting EC for B_k, which we call $EC_{res}(B_k)$. This $EC_{res}(B_k)$ serves as input (i.e. as $EC_{prev}(B_k)$) for the next step. Having completed the procedure for all areas $A_1, \ldots, A_n$, we get the final $EC_{res}(B_k)$. For the moment, we will refrain from discussing whether the order in which $A_1, \ldots, A_n$ are processed has any influence on the final result (see below and Appendix B).

It is important to note that the iterative procedure described above has to be applied only if $n > 1$, that is, if there is more than one area in map A' which is coextensive with area B of map B' (e.g. several sub-areas or overlapping areas). Only in this case, we need several steps to compute the resulting EC for area B. Thus, we call the respective operation 'multistep operation' or 'multistep mapping' (M_M). If, however, there is only one area A in map A' that is larger than or identical with area B of map B' (i.e. $RC(A, B) = L$ or $RC(A, B) = I$), then the procedure is much simpler. As we can perform the mapping process in one single step we do not need to take into account intermediate results such as our EC_{prev} above. Instead, all we need to know in this case is the relation between the two areas (i.e. $RC(A, B)$) and the information about area A (i.e. $EC(A)$). We call this function the 'single-step operation' or 'single-step mapping' (M_S).

For formal reasons, the multistep operation M_M requires an additional EC '*B*' to mark the special situation of the beginning of the transformation. As M_M is only necessary for transforming *S*- and *O*-relations (see above), it is generally defined as

$$M_M: (C_{EC} \cup \{B\}) \times \{S, O\} \times C_{EC} \rightarrow C_{EC}. \quad (1)$$

The single-step operation M_S for mapping identical or larger areas is generally defined as

$$M_S: \{I, L\} \times C_{EC} \rightarrow C_{EC}. \quad (2)$$

The exact specification of these mappings is given in tables 1 and 2.

Finally, it should be noted that the AT defined here is only one among several possibilities. It may vary in order to adapt to requirements of specific data modalities (for example, correct processing of explicitly absent projections in connectivity data requires additional ECs and transformation rules—see Appendix C). For the sake of simplicity, we here describe a basic version of a general AT whose operation M_M lacks commutative properties (see figure 4), that is, the final result of a transformation is not completely independent of the order in which the respective areas are processed by the AT. From a mathematical point of

Table 1. *Multistep operation M_M of* AT

This table specifies the definition of the multistep operation M_M: $(C_{EC} \cup \{B\}) \times \{S, O\} \times C_{EC} \rightarrow C_{EC}$ describing the constellations occurring during the transformation of information to an area B from several sub- or overlapping areas A_i $(i > 1)$. $EC_{prev}(B)$ denotes the information mapped to B in previous steps, $RC(A_i, B)$ denotes the relation between A_i and B, and $EC(A_i)$ denotes the information of A_i that is currently mapped to B. First three columns represent the triplet $(EC_{prev}(B), RC(A_i, B), EC(A_i))$, fourth column gives the resulting $EC_{res}(B)$.)

$EC_{prev}(B)$	$RC(A_i, B)$	$EC(A_i)$	$EC_{res}(B)$
	S	$\mathcal{N}$	$\mathcal{N}$
		P	P
		X	X
		C	C
	O	$\mathcal{N}$	$\mathcal{N}$
		P	U
		X	U
		C	C
	S	$\mathcal{N}$	$\mathcal{N}$
		P	P
		X	P
		C	P
	O	$\mathcal{N}$	$\mathcal{N}$
		P	U
		X	U
		C	P
	S	$\mathcal{N}$	U
		P	P
		X	X
		C	X
	O	$\mathcal{N}$	U
		P	U
		X	U
		C	X
	S	$\mathcal{N}$	P
		P	P
		X	P
		C	P
	O	$\mathcal{N}$	P
		P	P
		X	P
		C	P
	S	$\mathcal{N}$	P
		P	P
		X	X
		C	X
	O	$\mathcal{N}$	P
		P	X
		X	X
		C	X
	S	$\mathcal{N}$	P
		P	P
		X	X
		C	C
	O	$\mathcal{N}$	P
		P	X
		X	X
		C	C

iew, therefore, the procedure described above is not 'well efined'. Slight modifications of the simple AT described here, owever, are sufficient to render the operation M_M commutative nd to overcome this drawback (see Appendix B).

Table 2. *Single-step operation M_S of* AT

(This table specifies the single-step operation M_S: $\{I, L\} \times C_{EC} \rightarrow C_{EC}$ describing the transformation of information to an area B from an identical or larger area A. $RC(A, B)$ denotes the relation between A and B, $EC(A)$ denotes the information of A that is being mapped to B. First two columns represent the pair $(RC(A, B), EC(A))$, third column gives the resulting $EC_{res}(B)$.)

$RC(A,B)$	$EC(A)$	$EC_{res}(B)$
I	$\mathcal{N}$	$\mathcal{N}$
	P	P
	X	X
	C	C
L	$\mathcal{N}$	$\mathcal{N}$
	P	U
	X	U
	C	C

(c) *A formal description of the transformation process*

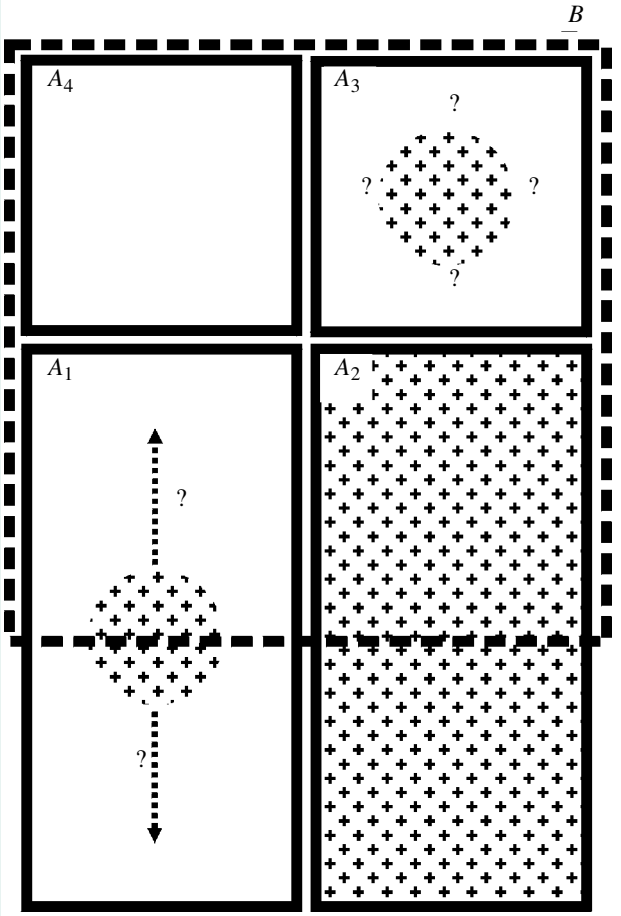
Based on the above introduction to the AT, the next two sections give a formal mathematical description of the entire transformation process between two areas of different maps. The formal accuracy of this and the following section is intended to give a guideline for implementation of ORT algorithms in databases. Readers who are interested in the main principles of ORT only may therefore skip these two sections.

Before starting with the formal description, however, a conceptual prerequisite is necessary in order to make mathematical conventions of set theory applicable to cortical areas. Within the following description, we envisage a 'standard brain' whose cortical surface ('standard cortex') is divided into a finite number of small patches each of which may be called an 'elementary micro-area' (EMA). These EMAs are thought to be small enough to lie within any of the areas that would result from simultaneous projection of all existing cortical maps on to the standard cortex. Each cortical area of any cortical map is thus equivalent to a finite, non-empty set of EMAs and accordingly, each brain map is treated as a finite, non-empty set of finite, non-empty sets of EMAs. In this way, we have defined some formal units that are compatible with operations from mathematical set theory. In the following, if an operation, such as union or intersection, is applied to cortical areas defined in this way, then this operation is understood as referring to the EMAs. For example, this convention allows us to describe two areas A and B of two different maps which are coextensive on the standard cortex in some way (i.e. $RC(A, B) \neq D$) by the statement $A \cap B \neq \varnothing$. Similarly, the situation of an area A in a cortical map A' being equivalent to two smaller sub-areas B_1 and B_2 in another map B' can be expressed as $A = B_1 \cup B_2$. Equipped with this conceptualization of cortical areas and cortical maps, we can now describe the transformation process formally.

Let A' and B' be two different parcellation schemes, i.e. two sets of cortical areas:

$$A' = \{A_1, A_2, \ldots, A_a\}, a \geqslant 1$$
$$B' = \{B_1, B_2, \ldots, B_b\}, b \geqslant 1. \qquad (3)$$

The general question now is: How can we transform information referring to a specific area A_α of map A' $(1 \geqslant \alpha \geqslant a)$ into information referring to one or several areas of map B'?



igure 4. A simple example for the use of the multistep peration M_M in a transformation process. Relations between reas A_1 to A_4 and B are $RC(A_1, B) = RC(A_2, B) = O$, $C(A_3, B) = RC(A_4, B) = S$. Information contained by A_1 to $_4$ is $EC(A_1) = P$, $EC(A_2) = C$, $EC(A_3) = X$, $EC(A_4) = N$. The erative transformation process includes a step for each area, sing the result from the previous step as input for the current ne: 1. $M_M(B, RC(A_1, B), EC(A_1)) = U$, 2. $M_M(U, RC(A_2, B), EC(A_2)) = X$, 3. $M_M(X, RC(A_3, B), EC(A_3)) = X$, 4. $M_M(X, RC(A_4, B), EC(A_4)) = P$. In one line, this can be ritten as $M_M(M_M(M_M(M_M(B, RC(A_1, B), EC(A_1)), C(A_2, B), EC(A_2)), RC(A_3, B), EC(A_3)), RC(A_4, B), C(A_4)) = P$ (compare equations (8*c*) and (8*d*)). This figure lso exemplifies the lack of commutative properties of M_M see Appendix B): if the areas are processed in the order –1–2–3, M_M does not deliver a partial EC but $EC_{res} = X$. his restriction, although not serious because of the similarity f partial and existing ECs, can easily be overcome by nhanced algebras with commutative properties (see ppendix B).

First, we have to determine to which areas of map B' the nformation of area A_α will be converted. In other words, we ave to find all areas B_k of B' which are coextensive with area $_\alpha$ in some way.

$$_B = \{B_k \in B' | B_k \cap A_\alpha \neq \varnothing, 1 \leqslant k \leqslant b\}. \quad (4)$$

or each area $B_k \in \Phi_B$, we now have to determine what informaon it will contain as a result of the transformation process. That , we have to find all areas A_j of map A' which are coextensive ith area B_k in some way and whose ECs must therefore be ntegrated by means of the algebra operations to yield a resulting C for B_k:

$$\Phi_A^k = \{A_j \in A' | A_j \cap B_k \neq \varnothing, 1 \leqslant j \leqslant a\}. \quad (5)$$

Please note that Φ_A^k is always defined with reference to the B_k for which the transformation is currently performed. Due to its definition and that of Φ_B, Φ_A^k at least contains A_α.

As the indices of the areas of Φ_A^k are not necessarily in consecutive order, we need a set of nested indices I^k to facilitate our operations on Φ_A^k (see equations (8*c*), (8*d*), (13) and (17) for examples).

$$I^k = \left\{ i_1, i_2, \ldots, i_n | (A_{i_1} \in \Phi_A^k, \ldots, A_{i_n} \in \Phi_A^k) \wedge \left(\bigcup_{x=1}^{n} A_{i_x} = \Phi_A^k \right) \right\} \subseteq \{1, 2, \ldots, a\}. \quad (6)$$

Φ_A^k is the minimal set of areas from A' that, as a unified piece of cortex, is identical with or contains B_k. Therefore, each of its constituent areas A_{i_x} $(1 \leqslant x \leqslant n)$ necessarily contributes to the information that B_k will have as the result of the transformation:

$$\left(\Phi_A^k = \bigcup_{x=1}^{n} A_{i_x} \right) \supseteq B_k \wedge ((\Phi_A^k \setminus \{A_{i_y}\}) \subset B_k) \quad (1 \leqslant y \leqslant n). \quad (7)$$

Depending on the relation between our initial area A_α and our currently investigated area B_k, we can now apply the appropriate algebra operation to each area of Φ_A^k. If the initial area A_α is identical with or larger than B_k, then A_α is the only member of Φ_A^k, so we apply the single-step operation M_S of the following algebra.

If $RC(A_\alpha, B_k) = I$, then
$|\Phi_B| = 1, |\Phi_A^k| = 1,$
$EC_{res} = M_S(I, EC(A_\alpha))$. (8*a*)

If $RC(A_\alpha, B_k) = L$, then
$|\Phi_B| > 1, |\Phi_A^k| = 1,$
$EC_{res} = M_S(L, EC(A_\alpha))$. (8*b*)

If the initial area A_α is a sub-area of or overlapping with B_k, then Φ_A^k has more elements than just A_α. We therefore iteratively apply the multistep operation M_M of the algebra, using the resulting EC from one operation as the input for the next (in the following two formulas, RC_{i_x} and EC_{i_x} are used synonymously for $RC(A_{i_x}, B_k)$ and $EC(A_{i_x})$, respectively).

If $RC(A_\alpha, B_k) = S$, then
$|\Phi_B| = 1, |\Phi_A^k| > 1,$
$EC_{res} = M_M(\ldots M_M(M_M(B, RC_{i_1}, EC_{i_1}), RC_{i_2}, EC_{i_2}) \ldots), RC_{i_n}, EC_{i_n})$. (8*c*)

If $RC(A_\alpha, B_k) = O$, then
$|\Phi_B| > 1, |\Phi_A^k| > 1,$
$EC_{res} = M_M(\ldots M_M(M_M(B, RC_{i_1}, EC_{i_1}), RC_{i_2}, EC_{i_2}) \ldots), RC_{i_n}, EC_{i_n})$. (8*d*)

Figure 4 shows a simple example how this formal description can be understood in practice.

(d) *Specific problems of transforming connectivity data*

Connectivity data play a key role in analyses of brain organization and thus also in attempts to establish databases (see § 1). Therefore, we describe the main principles of how ORT

an be adapted to this specific class of brain data. Transforming onnectivity data requires specific considerations for the simple eason that we do not deal only with a source map and target ap between which transformation takes place, but every rojection also consists of a source and a target area. Their nformation must be transformed separately while nevertheless onsidering their mutual context. In essence, there are three ain points.

First, the principles of transformation outlined above have to e applied to both the source and target area. The resulting Cs can then be put together to yield a so-called projection ode (PrC). However, the ECs of the injected site and of the abelled site (anterograde tracer: injection in the source area of he projection, label in the target area of the projection; retro- rade tracer: vice versa) bear slightly different meanings. The C of the injected site describes only the spread of injected racer substance and does not state which proportion of omata–terminals from the injected site actually take up and ransport tracer substance to the labelled area. On the ontrary, the EC of the labelled site describes the actual extent f somata–terminals within the labelled area that receive asso- iation fibres from the injected site. Furthermore, many tracer udies have demonstrated that association fibres from an area to another area B often do not originate throughout the hole extent of A (for example, see Bates & Goldman-Rakic 993; Luppino *et al.* 1993). This means that injections of ifferent extent and position within the injected site may lead o different and seemingly contradictory ECs of the labelled te. For example, a partial injection of anterograde tracer into rea A might fail to produce label in area B. However, this oes not preclude that a partial anterograde injection into nother subpart of A or a complete anterograde injection into rea A might lead to labelling of area B. In large databases omprising many different studies, such difficulties can be vercome by data-mining methods in combination with ORT. lthough a detailed description of such methods is beyond the mits of this article, one option is to analyse redundant reports n both antero- and retrogradely traced projections. Such an pproach has been implemented in the database CoCoMac- racer (see § 4).

Second, projections that are explicitly stated to be absent (i.e. $EC = \mathcal{N}$ for the labelled area) require additional steps to prevent onversion of absent projections into existing ones (false posi- ves) or vice versa (false negatives) (see Appendix C for more etails).

Third, any given area $A_j \in \Phi_A^k$ contains different information .e. different ECs) in the context of different projections. We herefore need to describe formally which ECs of all the projec- ons that A_j participates in are integrated for a given area $_k \in \Phi_B$. Thereby it has to be distinguished whether B_k is the ource area or target area of the projection being transformed. his section describes the process in a formal way.

Assume that we intend to transform the projection

$$_\alpha{:}A_p \xrightarrow{\mathrm{EC}(A_p)\mathrm{EC}(A_q)} A_q (1 \leqslant p, q \leqslant a) \tag{9}$$

om map A' to map B'. Dealing with the transformation of the nformation of the source area A_p first, we have

$$_B = \{B_s \in B' | B_s \cap A_p \neq \varnothing, 1 \leqslant s \leqslant b\} \tag{10}$$

as the set of those areas in map B' which overlap in some way with the source area A_p of our projection P_α. Then for each area $B_s \in \Sigma_B$ we determine

$$\sum\nolimits_A^s = \{A_f \in A' | A_f \cap B_s \neq \varnothing, 1 \leqslant f \leqslant a\} \tag{11}$$

as the set of those areas in map A' which overlap in some way with area B_s. Please note that in analogy to equation (5), Σ_A^s is always defined with reference to the area B_s for which the transformation is currently performed. Due to its definition and that of Σ_B, Σ_A^s at least contains A_p.

In correspondence with equation (6), we now determine the index set Γ^s for the areas of Σ_A^s:

$$\Gamma^s = \left\{ i_1, i_2, \ldots, i_n | (A_{i_1} \in \Sigma_A^s, \ldots, A_{i_n} \in \Sigma_A^s) \wedge \left(\bigcup_{x=1}^{n} A_{i_x} = \Sigma_A^s \right) \right\} \subseteq \{1, 2, \ldots, a\} \tag{12}$$

Now we can list the projections $\Omega_1, \ldots, \Omega_n$ originating from the areas in Σ_A^s and terminating at the target area A_q of our initial projection P_α (note that $\exists v, 1 \leqslant v \leqslant n{:}\Omega_v = P_\alpha$):

$$\Omega_1{:}A_{i_1} \rightarrow A_q, \ldots, \Omega_n{:}A_{i_n} \rightarrow A_q. \tag{13}$$

The ECs of the source areas of these projections are then integrated iteratively by the algebra operations (see equations (8*a*)–(8*d*)) that yield the resulting $\mathrm{EC}(B_s)$.

We proceed correspondingly for the target area A_q of our projection P_α:

$$T_B = \{B_t \in B' | B_t \cap A_q \neq \varnothing, 1 \leqslant t \leqslant b\}, \tag{14}$$

$$T_A^t = \{A_g \in A' | A_g \cap B_t \neq \varnothing, 1 \leqslant g \leqslant a\}, \tag{15}$$

$$\Gamma^t = \left\{ j_1, j_2, \ldots, j_m | (A_{j_1} \in T_A^t, \ldots, A_{j_m} \in T_A^t) \wedge \left(\bigcup_{y=1}^{m} A_{j_y} = T_A^t \right) \right\} \subseteq \{1, 2, \ldots, a\}. \tag{16}$$

The projections $\Psi_1, \ldots, \Psi_m$ originating from the source area A_p of P_α and terminating in the areas of T_A^t are the following (note that $\exists w, 1 \leqslant w \leqslant m{:}\Psi_w = P_\alpha$):

$$\Psi_1{:}A_p \rightarrow A_{j_1}, \ldots, \psi_m{:}A_p \rightarrow A_{j_m}. \tag{17}$$

The ECs of the target areas of these projections are then integrated by the algebra operations (see equations (8*a*)–(8*d*)) that yield the resulting $\mathrm{EC}_{\mathrm{res}}(B_t)$.

Having computed a resulting EC for each $B_s \in \Sigma_B$, and for each $B_t \in T_B$, we finally determine the Cartesian product $\Sigma_B \times T_B$:

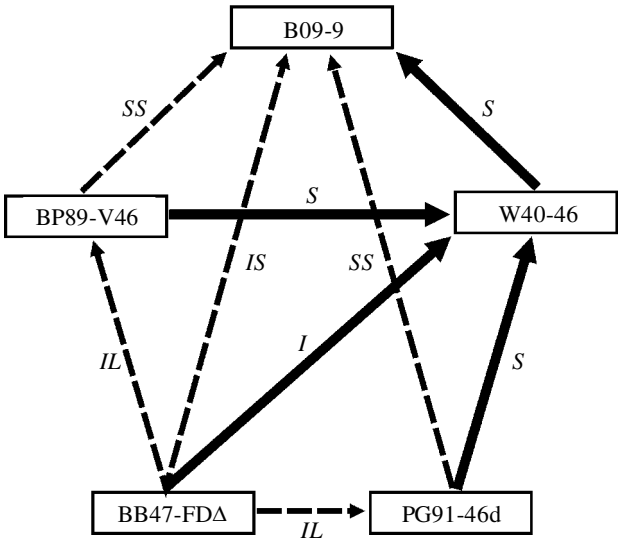
$$\Theta(P_\alpha) = \Sigma_B \times T_B = \{(B_s, B_t) | B_s \in \Sigma_B, B_t \in T_B\}. \tag{18}$$

The set $\Theta(P_\alpha)$ comprises all projections in map B' which result from the transformation of the projection P_α in map A'. To further specify these projections we determine their PrCs by simply concatenating the ECs of their source and target areas (see Appendix A for the definition of the concatenation operator •):

$$\mathrm{PrC}(B_s, B_t) = \mathrm{EC}(B_s) \bullet \mathrm{EC}(B_t) \quad (B_s \in \Sigma_B, B_t \in T_B). \tag{19}$$

(e) *The problem of unknown relations*

The principles described so far presume that the relations (i.e. RCs) of the concerned areas are known. Unfortunately, each author introducing a new parcellation scheme can at best compare the new map to a few others, leaving the large majority



igure 5. A simple example of a transformation graph onsisting of five areas. Abbreviations are as follows: 09–9, area 9 of Brodmann (1909); BB47-FDΔ, area FDΔ f von Bonin & Bailey (1947); BP89-V46, area V46 of arbas & Pandya (1989); PG91-46d, area 46d of Preuss & oldman-Rakic (1991*a*); and W40-46, area 46 of Walker 1940). Edges are represented by bold and broken arrows. old arrows designate initially known relations between reas, broken arrows show initially unknown relations that re deduced by graph-theoretical optimisation. Labels of rrows designate the transformation path codes. Note that or each pair of related areas, this figure shows only one elation–arrow; the reverse relations–arrows have been left ut to maintain clarity of the diagram.

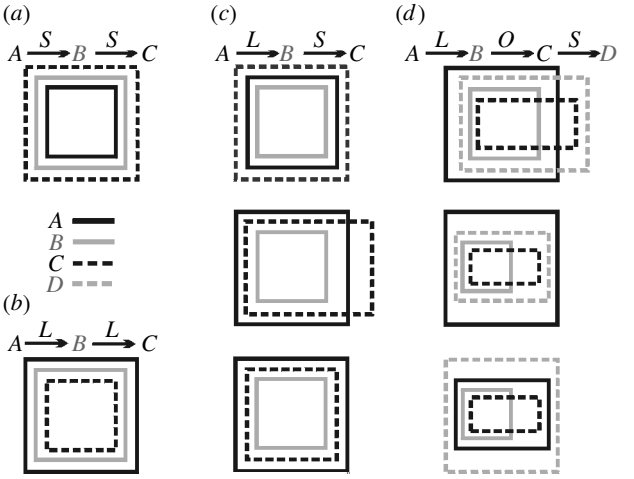


Figure 6. Examples of valid transformation paths. (*a*) A path represented by the transformation path code *SS* (path category L_2). (*b*) A path represented by the transformation path code *LL* (path category L_3). (*c*) Three paths, each represented by the transformation path code *LS* (path category L_4), demonstrate that a sequence of *L*- and *S*-relations represents a valid path, but can yield three different resulting relations ($RC_{res}(A, C) = S/O/L$). (*d*) Three paths, each represented by the transformation path code *LOS* (path category L_4), demonstrate that the additional occurrence of a single *O*-relation between sequences of *L*- and *S*-relations still maintains validity and yields the same three different resulting RCs as for (*c*).

f existing parcellation schemes unmentioned. Consequently, our nowledge about the relations of arbitrary pairs of maps is rather mited. We therefore need a method to infer new knowledge from xisting knowledge, that is, to deduce relations hitherto nknown from the ones described in the literature.

ORT incorporates such a method based on graph-theoretical oncepts. The main principle is to represent all available knowlge about areas from different maps and their relations as a raph, i.e. as a set of nodes connected by a set of edges. In our ase, the nodes represent all areas of all known maps and two odes are connected by an edge if there is a known relation etween the respective areas. We call such a graph a transforma- on graph (figure 5 shows an example) and any sequence of odes being connected by edges a transformation path (see ppendices D and G for the precise definitions).

If we want to derive an unknown relation between two areas and C of different maps (i.e. a missing edge between two odes A and C of the transformation graph), we must try to find bypass via intermediate nodes $B_1, \ldots, B_n (n \geqslant 1)$. In other ords, similar to a driver who copes with an unfamiliar route om city A to city C by consecutively choosing familiar routes om city A to city B_1, from city B_1 to city B_2, . . ., from city B_n o city C, we have to find a transformation path that connects he nodes A and C indirectly.

For this purpose, we have adapted a standard algorithm from raph-theory ('all-pairs-shortest-path' algorithm by Floyd), hich determines optimal paths between all pairs of nodes Floyd 1962; Güting 1992). Adapting this algorithm to the pecific conditions of our transformation graph was aggravated y two main problems:

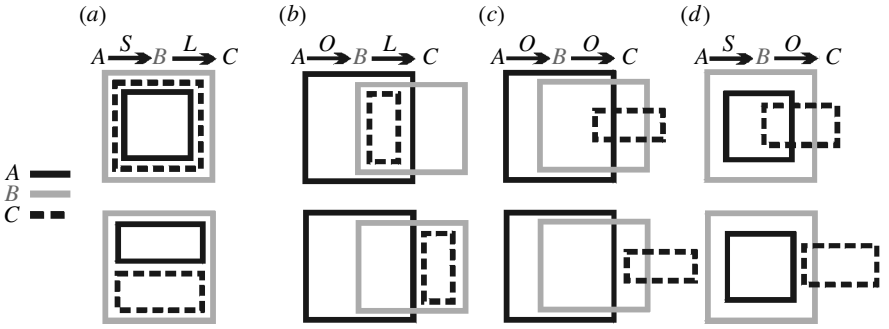
(i) Validity: as some sequences of RCs do not allow unambiguous interpretation (see §2(f)), not all transformation paths are a valid expression for an unknown relation. Therefore, we need an effective method to decide whether a given transformation path is ambiguous or not.

(ii) Optimality: at each step, Floyd's algorithm compares all possible alternative paths between two given nodes according to a given measure of optimality (see §2(f)). We need to define such a measure of optimality that is appropriate for our context.

We will describe our solution to these problems first, then give a description of our adaptation of Floyd's graph-algorithm.

(f) *Validity and optimality of transformation paths*

As mentioned above, there can be difficulties when we try to derive an unknown relation between two areas A and C of different maps by finding a transformation path via intermediate areas $B_1, \ldots, B_n$ of n different maps ($n \geqslant 1$). This problem is due to the fact that the RCs (which define the edges of the path) abstract from the exact spatial locations that two areas of different maps would have on a standard cortex. Certain sequences of relations can therefore be interpreted ambiguously. For example, envisage two areas A and C of different maps A' and C' whose relation we do not know. Suppose further that we know an area B of a map B' which overlaps with both area A and area C (i.e. $RC(A, B) = O$; $RC(B, C) = O$). Unfortunately, this information does not help us: depending on the absolute spatial extent of the twofold overlap, areas A and C can either still overlap or be completely disjoint (see figure 7*c*). In addition to this case, there are some further constellations that also lead to ambiguous results (figure 7 illustrates this schematically).



igures 7. Examples of invalid transformation paths (path category L_0). For each of the paths (*a*)–(*d*) the upper row shows ossible spatial configurations of the involved areas for which some coextension of the first and last area is present. The lower row emonstrates that the areas of the same path may have relative positions for which the first and last area are no longer oextensive on standard cortex.

To deal with this problem, ORT uses methods from theoretical computer science: formal languages and finite automata (see Appendices E and F for details of all following descriptions). The main principle is to identify each transformation path by the word that is created by concatenating the RCs of its edges. Regarding the RCs thus as an alphabet, we define a formal language L whose words are created by all possible combinations of RCs; these words (transformation path codes) then represent all potential transformation paths. We can subdivide into two subsets: one subset L_+ comprises words representing valid (unambiguous) transformation paths (figure 6); another subset L_0 contains words representing invalid (ambiguous) transformation paths (figure 7). We are then able to define a finite automaton which reads step by step any given word $w \in L$ and decides whether it belongs to L_+ or to L_0 and thus whether the transformation path represented by w is valid or not. Further specification is achieved by subdividing L_+ into five subsets L_1 to L_5, the path categories. These represent transformation paths with equivalent structure, i.e. transformation paths are equal within and are different between path categories with respect to their probability of creating ambiguous constellations for the AT. For example, a path consisting of an arbitrary number of *S*-relations will never lead to ambiguities, whereas a path with a single *O*-relation may well do (see table). The finite automaton can be easily constructed to decide for any given word from L to which of the six formal languages L_0 to L_5 it belongs (see figure 8 for visualization of the automaton). By ordering the path categories according to their potential of creating ambiguities for the AT, we obtain a hierarchy of optimality that allows us to choose between two alternative paths connecting the same nodes (see Appendices E and for the exact definitions).

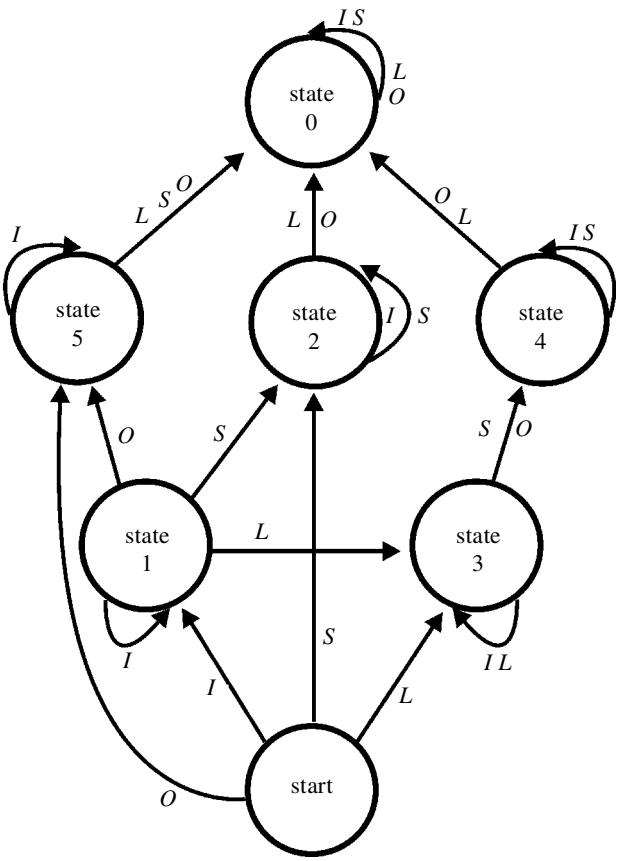


Figure 8. A finite automaton for the detection of valid and ambiguous transformation paths. Beginning at state 'START', the automaton reads a given word $w \in L$ representing a transformation path. Each RC evokes changes of state as indicated by the labels of the arrows. The index of the state in which the automaton terminates corresponds to the index of the path category to which the word w belongs.

(g) *Graph-theoretical deduction of formerly unknown relations*

We now briefly summarize the principle of Floyd's algorithm and our adaptation for the deduction of new relations (see Appendix H for details). For n areas of all known maps, the initial transformation graph G_0 consists of n nodes ($n \geqslant 1$) which are connected by an edge whenever a relation is known for the respective two areas. In G_0, the edges are thus designated by the RCs of the respective relations. Starting with this initial condition, the algorithm computes a sequence of graphs G_0, $G_1, \ldots, G_n$ using transformation path codes for the insertion of new edges and the substitution of existing ones by more favourable paths (note that the set C_{RC} is a subset of L_+, i.e. RCs are transformations path codes with a length of 1). At each step, G_i results from modification of G_{i-1}: evaluating every possible combination of predecessors v_j ($j \geqslant 0$) and successors w_k ($k \geqslant 0$) of node i in the graph G_i, the algorithm determines whether the intermediate node i may be used either to establish a hitherto non-existing edge (v_j, w_k) or to relabel an already existing edge (v_j, w_k). In both cases, the edge (v_j, w_k) is designated by the concatenation of the transformation path codes of the edges (v_j, i) and (i, w_k). Also, the algorithm stores the actual sequence of

reas $v_j, \ldots, i, \ldots, w_k$ by which the nodes v_j and w_k are onnected (using this sequence, the AT can later transform infor- nation from area v_j to area w_k via the intermediate areas). After steps, the optimized transformation graph G_n is produced, hich contains all valid transformation paths with a minimal otential of ambiguity (see Appendix H and the example in gure 5).

Finally, it should be noted that conflicting information about he relations of areas can lead to logically contradictory trans- ormation paths within the graph. For example, an area A of ap A' may be stated by one author to be a sub-area of area B_1 map B' whereas another author may consider the same area to be a sub-area of area B_2 in the same map B'. These state- ents obviously exclude each other logically. Therefore, it is ecessary to investigate the results of the graph-theoretical ptimization for inconsistencies and eliminate them from the raph (see Appendix J for details).

3. PRACTICAL BENEFITS OF ORT: TWO EXAMPLES

Having described the theoretical principles of ORT, we emonstrate its practical benefits with the help of two xamples. These examples are of complementary char- cter by illustrating how (i) the same data set can be ransformed to different parcellation schemes, and how ice versa (ii) different data sets can be transformed to he same parcellation scheme.

(a) *Same data source, different target maps*

First, we show how ORT can be used for differentiation nd control of analyses by juxtaposing results from an nalytical study on the functional connectivity of primate erebral cortex (Stephan *et al.*, this issue). Using three ndependent methods of analysis, this study demonstrated he highly clustered structure of the functional cortical etwork. The analyses were based on the database oCoMac-Stry, which contains data on functional onnectivity in macaque cortex (see §4). With the help of RT, the original data were transformed to two different arcellation schemes: one was the less-known parcellation f McCulloch (1944), the other one was a 'hybrid map' omposed of the well-known and still widely used parcel- ations of Walker (1940) for the prefrontal cortex and von onin & Bailey (1947) for the rest of the cortex. For onvenience, we here designate these two data sets as the *M*-data' (McCulloch) and '*H*-data' (hybrid), respectively. xactly the same analyses were applied to both data sets. hile Stephan *et al.* (this issue) presented only the results rom the *H*-data, we here directly juxtapose results from alanced optimal set analysis (OSA; see Hilgetag *et al.* 998; Hilgetag, Burns, O'Neill, Scannell & Young, this sue, for details) on binarily classified data. The compar- son of the two resulting clusterplots (figure 9*a*,*b*) reveals hat, while the results were generally compatible, each ata set offered slightly different perspectives. Both gures clearly show the principal clusters of the functional etwork that constantly emerged from all analyses erformed by this study: orbitofronto-temporal, visual nd somatomotor clusters. Without going into detail, it is pparent, however, that the intrinsic composition of these lusters showed variations between the two data sets compare figure 9*a* and *b*). For example, the visual cluster, hich is a unified block in the *H*-data, is split into two parts in the *M*-data. In the latter, the primary visual cortex (area 17) clusters more strongly with temporal visual areas surrounding the superior temporal sulcus (areas 21, 22), whereas the extrastriate areas are part of a second visual cluster (areas 18, 19, 20, 37). Interestingly, a discernible, but rather unobtrusive feature of the *H*-data became more obvious and differentiated in the *M*-data: a fourth small medio-frontal cluster of the *H*-data (fronto- polar area 10 and subcallosal area FL) also appeared for the *M*-data (areas 10 and 25), but additionally contained several lateral and medial prefrontal areas (areas 8, 9, 32, 46) as well as anterior cingulate cortex (area 24).

These differences illustrate that for a given set of data, each target map has a specific set of 'critical' areas for which mapping will be more difficult, due to their rela- tions with corresponding areas of other maps. Mapping the same set of connectivity data to different target maps by ORT therefore produces networks with local variances. Analyses using ORT-transformed data can effectively control uncertainty about potential transfor- mation-evoked distortions of the data by performing identical analyses simultaneously on several data sets that were mapped from the same source to different parcellation schemes. This approach allows us to scrutinize the results of the analyses from different perspectives and to assess their dependence on the trans- formation process.

(b) *Different data sources, same target map*

As a second example, we illustrate the role of ORT for the investigation of structure–function relationships. In the following example, we juxtapose data on structural and functional connectivity for the areas of the somato- motor and visual cluster, which resulted from OSA of functional connectivity in the macaque cerebral cortex (see §3(a)). The data on anatomical association fibre connectivity (figure 10*a*) were taken from the database CoCoMac-Tracer, the data on functional connectivity (figure 10*b*) from the database CoCoMac-Stry (see §4). Both data sets were transformed by ORT into the same parcellation scheme, i.e. the areas of the somatomotor and visual cluster in the hybrid map (see figure 9*a*) and were thus made directly comparable. First, this allows us to investigate the similarities and differences between the two data sets by simple inspection. For example, the two matrices exhibit interesting differences for the parietal areas that show stronger functional interactions with the somatosensory areas (see figure 10*b*), although anatomic- ally, they are more strongly connected with the visual areas (figure 10*a*). Second, and much more importantly, analytical or modelling approaches to the complex structure–function relations of cerebral cortex (for example, Kötter & Sommer, this issue) are greatly facilitated when the parcellation problem is removed by appropriate databases. The simple example illustrates how ORT combined with powerful databases can contribute to improving this situa- tion. Finally, it should be noted that the matrices as displayed here are just a 'snapshot' of the underlying databases as at January 1999, especially the database CoCoMac-Tracer, which still contains considerable 'white spots' for certain cortical areas (see figure 10*a*), and is continually being improved and extended to finally deliver a full account of the structural cortical network in the macaque.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

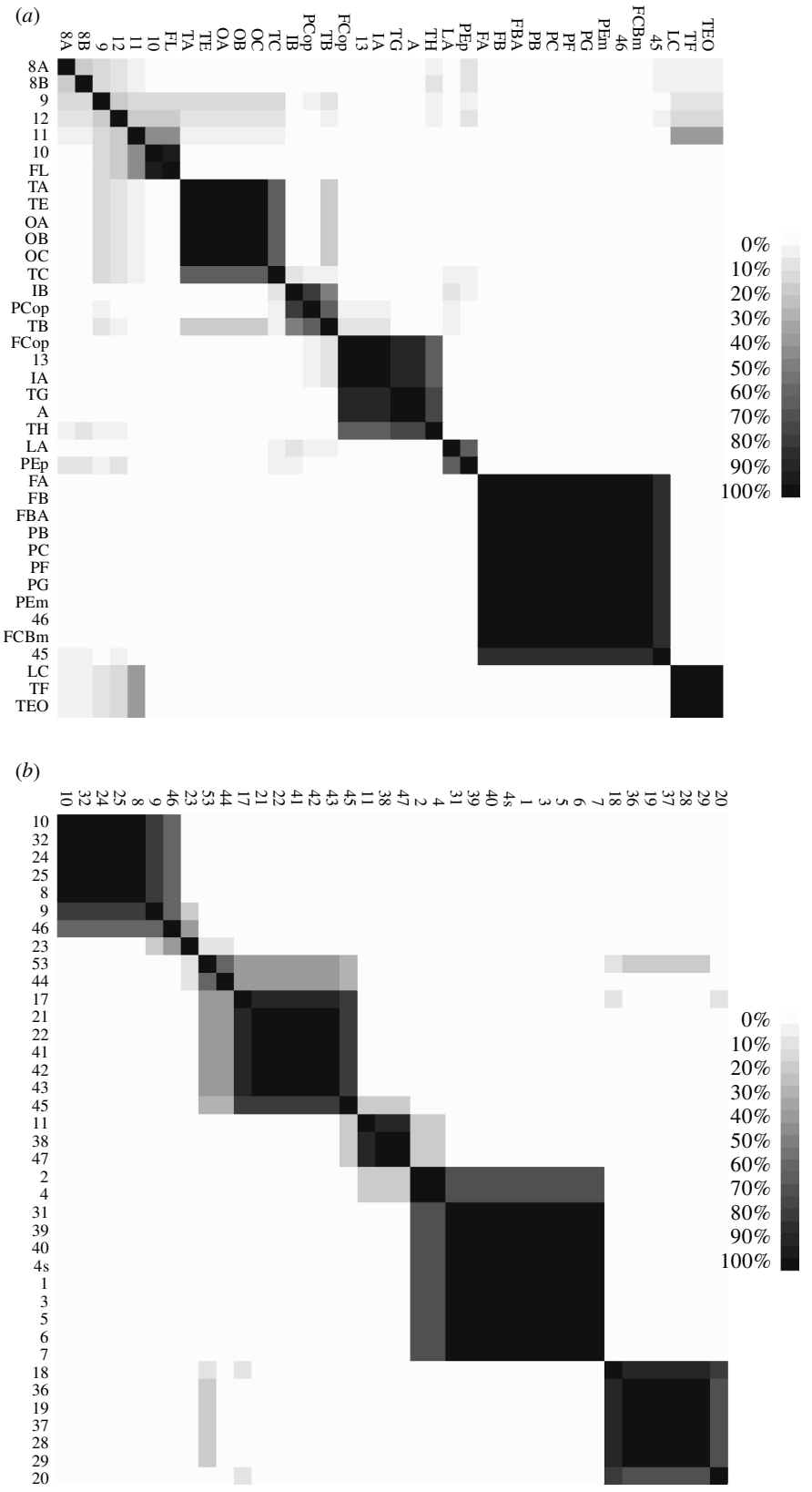


Figure 9. Two clusterplots resulting from optimal set analysis (OSA; see Hilgetag, Burns, O'Neill, Scannell & Young, this issue, for details) under balanced conditions for the same data set (binarily classified data on functional connectivity in macaque cerebral cortex; see Stephan *et al.*, this issue, for details). Data matrices have been ordered to optimally reflect the cluster configuration of both results. Intensity of shading indicates relative strengths of association for pairs of areas. Note that both results demonstrate the same general cluster configuration, i.e. predominant orbito-temporal, visual, and somatomotor clusters, but show slightly varying composition of these clusters. (*a*) OSA results for data transformed by ORT to a hybrid map combining Walker's (1940) and Von Bonin & Bailey's (1947) maps. (*b*) OSA results for data transformed to the map of McCulloch (1944).

(*a*)

	FA	FB	FBA	FCBm	46	PB	PC	PEm	PEp	PF	PG	TA	TE	TEO	TF	OA	OB	OC
FA		1	1	1	0	0	1	0	0	1	0	0	0	0		0	0	0
FB	1		1	1	1				0		0							
FBA	1	1		1	1		1	0	0	1	0	0	0	0		0	0	0
FCBm	1	1	1		1			0	0	1	0	0	0	0		0	0	0
46	0	1	1	1							1	1	1		1	1	0	0
PB	0						1	0	0									
PC	1	1	1			0												
PEm	0	1	0	0					1		1	1	0	0		1		0
PEp	0		0	0				1			1	0	0	0	0	1	0	1
PF	1	1	1	1			1				0							
PG	0		0	0	1			1	1			1	1	0	1	0	1	1
TA	0		0	0	1			1	0		1		1	1	1	1	0	0
TE	0		0	0	1			0	0		1	0		1	1	0	1	1
TEO	0		0	0	1			0	0		1	1	1			1	1	1
TF					1			0	0		1	1	1	1		0	1	1
OA	0		0	0	1			1	1		1	1	0	1	0		1	1
OB	0		0	0	0			1	1		0	1	0	1	0	1		1
OC	0		0	0	0			0	1		0	0	0	0	0	1	1	

(*b*)

	FA	FB	FBA	FCBm	46	PB	PC	PEm	PEp	PF	PG	TA	TE	TEO	TF	OA	OB	OC
FA		1		1			1	1		1	1							
FB	1			1	0		1	1	1	1	1	0	0	1	0	1	1	0
FBA																		
FCBm	1	1			0		1	1	1	1	1	0	0	1		1	0	0
46	0	1	1	1			0	1	1	1	1	0		1		1	0	
PB	1	0	1	1	0		1	1	0	1	1	1	0	0		0	0	0
PC	1	1		1				1		1	1							
PEm	1	1	0	0	1		1		1	1	1	1	1	1		1	1	1
PEp	1	1	0	0	0		1	1		0	0	0	0	0	0	1	1	1
PF	1	1	1	1	1		1	1	0		1	1	0	1		1	1	1
PG	1	1	1	0	1		1	1	0	1		1	0	1		1	1	1
TA	0	0	0	1	1		0	0	0	1	0		1	1		1	1	1
TE	0	0	0	0	1		0	0	1	1	1	1		0	1	1	1	1
TEO	0	0		0	0		0	0	1	0	1	0	1		1	1	1	0
TF	0	0	0	0	0		0	0	0	0	1	0	1	1		1	0	0
OA	0	0	0	0	0		0	1	0	1	1	1	1	1			1	1
OB	0	0		0	0		0	0	0	0	1	0	1	0	1	1		1
OC		0							0	0	0			0	0	0	1	

igure 10. Two matrices resulting from transformation of natomical and functional connectivity data, respectively, to ne same map by ORT. Connections–functional interactions hose existence were demonstrated experimentally are esignated as 1, those which have explicitly found to be bsent are designated as 0. Matrices have been ordered dentically to allow a direct comparison. The areas shown elong to the somatomotor and visual clusters of figure 9 and re named according to a hybrid map comprising the arcellations of Von Bonin & Bailey (1947) and Walker 1940). (*a*) Matrix of association fibre connectivity data from ne database CoCoMac-Tracer. Area names along the vertical xis represent source areas, whereas area names along the orizontal axis designate target areas of anatomical rojections. (*b*) Matrix of functional connectivity data from ne database CoCoMac-Stry. Area names along the vertical xis represent stimulated areas, whereas area names along the orizontal axis designate recorded areas.

4. DISCUSSION

ORT is a simple, yet effective method by which the arge amount of already published data can be transformed into a common, descriptive space. The foremost aspect of ORT is its coordinate-independence: mapping is performed without an absolute spatial reference system but is instead based on published statements about relative positions of areas in different maps (RCs). This property accounts both for strengths and limitations of ORT that we now discuss in more detail.

Beginning with the limits, in spite of all optimization some EC–RC-constellations remain which yield no unambiguous result for the algebra of transformation (see tables 1 and 2). Although they are few and their occurrence is minimized by the graph-theoretical optimization leading to transformation paths with least likelihood of such constellations, they cannot be eliminated completely. For most practical applications of ORT, however, this is no serious restriction because the problem diminishes for large data sets with many parcellation schemes and a high degree of information redundancy. Such data sets result, for example, from the collation of anatomical or functional connectivity data from the numerous published studies (see Stephan *et al.*, this issue). In these cases, most pieces of information are at least partially mirrored by data based on other maps. It is therefore very likely that the impossibility to transform an individual datum is compensated by transforming the equivalent data from other maps.

Furthermore, one might question the validity of statements concerning the relative positions of areas in different maps, that is the RCs. A potential problem is that such statements found in the literature can have very different backgrounds. For example, some relations result from simple topographical comparisons of different brain maps. These comparisons usually determine the relative position of areas by relating them to morphological landmarks such as sulci. Sulci, however, are known to possess high inter-individual variability and lack a consistent correlation with cytoarchitectonically defined areal borders (Zilles *et al.* 1997). Therefore, these comparisons can be problematic, at least if they concern areas of small size. Many other comparisons, however, are based on actual experimental investigations that established the relation of two different parcellation schemes with high certainty. For example, such experiments lead to the subdivision of architectonically defined areas due to differences in transmitter and enzyme distributions, electrophysiological properties or connectivity patterns (as examples, see Carmichael & Price 1994; Geyer *et al.* 1996; Matelli *et al.* 1991). In this context, it should be emphasized that the 'objectivity' of ORT does not mean to imply that ORT-mapped data are 'objectively correct'. Like previous databases, ORT depends on a set of subjective notions from different authors about the relations between different brain maps. However, these relations and their algorithmic processing are formalized (RCs and AT), their collation from the literature is operationalized (see codes for the precision of data description below) and within ORT-based databases they are explicitly represented and linked to exact references in the literature. Whenever the same set of relations is used for transforming data by ORT, the same result will be delivered, irrespective of any observer performing the mapping. This observer-independency of the transformation on the basis of a given set of relations is what we denote by the term 'objective' in the acronym ORT. Also, for any given transformation, the relations that were used and in

hat way, are explicitly represented, thus the mapping rocess is fully transparent.

Coordinate-independence is not only responsible for otential problems of ambiguity, but also affords nportant advantages of ORT. It accounts for the rela- vely simple, yet effective, principles of ORT that can asily be incorporated in algorithms within neuro- cientific database systems (see below). Most importantly, oordinate-independence ensures that ORT makes very ew demands on the data it transforms. All it requires is hat they are described on the basis of a known parcella- on scheme. Only in this way can the huge amount of ata from already published studies (e.g. tracer studies) e made accessible and comparable by their organization n powerful databases.

Another question that should be addressed is whether ORT is equally suitable for different modalities of brain ata. ORT, as it is described here, is primarily designed or brain data of binary nature on a nominal scale (e.g. xistence or non-existence of transported tracer ubstance in a given area). For such data, the necessary lgebra of transformation is relatively simple to define see tables 1 and 2). It becomes more complicated if ealing with data that are still on a nominal scale but now more than two disjoint classes (e.g. laminar atterns of transported tracer substance). These cases can till be coped with by extending the operations of the lgebra to include an additional factor (e.g. a code for he laminar pattern), thus accounting for the special roperties of the transformed data. In this way, the lgebra operations do not only deliver a resulting EC but lso specify how the information as such is affected by he transformation. Other data types that are measured n metric scales, such as quantitative measurements of nzyme or receptor densities, however, seem to be eyond the scope of ORT. Although scale transforma- ons may prove useful for such conditions (e.g. transfer- ing metric data to a nominal scale by applying an ppropriate threshold), a large proportion of the original nformation would be lost. Therefore, metric data equire absolute spatial reference systems because the egree of spatial overlap quantitatively determines the utcome of the transformation.

Currently available spatial methods of mapping brain ata are parts of conventional or electronic atlas systems Mazziotta *et al.* 1995*a*,*b*; Roland & Zilles 1996; Talairach Tournoux 1988). A major issue addressed by these nore recent approaches is the intersubject spatial varia- ility of the human brain. The classical brain maps from he beginning of the 20th century were based on the nalysis of one or a few brains, and the maps were resented as schematic drawings. Thus, such maps cannot e used for spatial mapping purposes and do not reflect ntersubject variability. However, even if the mapping is erformed by a real three-dimensional representation of ata, the problem of intersubject anatomical variability ust be solved. This is presently done by the development f techniques that allow the linear and/or nonlinear eformation of the three-dimensional data set of an indi- idual brain into a spatial reference system, e.g. an indivi- ual 'standard' brain or an 'average' brain constructed rom a large sample of individual brains. Presently, these patial maps are under development and contain only a few architectonically defined cortical units (Roland & Zilles 1996).

There is yet another, very general, problem that should be briefly discussed in this context, that is the integration of data from different sources. Data from different studies may not only result from different methods and may thus have different degrees of reliability, but they also show obvious differences in the precision of data description. Due to the complicated nature of this problem, we can only briefly discuss some implications for neuroscientific databases. We would like to point out especially that the implementation of ORT within a given database system may vary depending on the way in which this problem is handled. Since it is difficult to assess the reliability and correctness of published data, one might instead try to establish a measure for potential errors in data collation due to imprecise and ambiguous presentation. Such a measure can be of particular importance when one has to decide between alternative (and possibly conflicting) reports for the same data. A possible approach is to define clear criteria for measuring the precision of data description in an individual publication on ordinal scale as objectively and reproducibly as possible. We developed such a measure (so-called PD codes; see Appendix I for a brief description) and have used it for data coding within two databases (see below). In these databases, we also used the PD codes in connection with the graph-theoretical optimization within ORT to facilitate the decision between alternative paths. PD coding and its use within databases will be described in detail in a forthcoming publication.

Finally, we would like to summarize in what way ORT has been practically used so far. As mentioned above, we have integrated ORT into two databases on structural and functional cortical connectivity in the cerebral cortex of the macaque (CoCoMac-Tracer and CoCoMac-Stry, respectively). CoCoMac-Stry contains almost 4000 experimental findings from studies of strychnine neuronography (see Stephan *et al.*, this issue for details) and has been used for a global analysis of the functional cortical network (Hilgetag *et al.* 1997; Stephan *et al.*, this issue). CoCoMac-Tracer, still under construction, currently contains more than 10 000 reports about association fibre connectivity from tracer studies, more than 150 different parcellation schemes and more than 2200 relations between areas of different maps. This database is being used for both experimental and theoretical studies, including biologically realistic computer simulations, network analyses, and functional imaging studies. Recently, it has been used for the analysis of imaging data in a study on the prefrontal cortex (Northoff *et al.* 2000). More information will soon be available at http://www.cocomac.org. In both databases, ORT has proven to be an effective, easy-to-use approach that helps to overcome the parcellation problem. Thus, these databases fulfil the five criteria we formulated at the beginning: objectivity, reproducibility, transparency, flexibility and simplicity. We believe that databases like these will play an increasingly important role in higher-order analyses of the structural and functional organization of the brain and for the investigation of structure–function relations. The challenge will be to extend ORT to other modalities than binary data and to continue the development of spatial methods which allow transformation of quantitative data on a metric scale.

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APPENDIX A. GENERAL DEFINITIONS

Within this article, we have adopted the nomenclature f Hopcroft & Ullman (1979), Güting (1992) and Rozen-erg & Salooma (1997) for formal languages, finite auto-nata and graphs. We here give a brief summary of some efinitions which are fundamental for an understanding f this appendix.

An alphabet Σ is a finite, non-empty set. The elements f an alphabet Σ are called letters or symbols. A word over n alphabet Σ is a finite sequence of n letters ($n \geqslant 0$), ncluding the empty word ε. Note that according to this efinition, letters are words of the length 1. If $x = x_1x_2 \ldots x_n$ nd $y = y_1y_2 \ldots y_m$ ($n,m \geqslant 0$) are words over an alphabet Σ, o is their concatenation $x \bullet y$ (or simply xy) obtained by riting x and y one after another: $x \bullet y = xy = x_1x_2 \ldots x_ny_1y_2 \ldots y_m$. For a given alphabet Σ, the set of all possible ords over Σ (including the empty word ε) is defined as Σ^* nd the set of all non-empty words over Σ as $\Sigma^+ = \Sigma^* \setminus \{\varepsilon\}$. Observe that Σ^* and Σ^+ are always infinite. A (formal) anguage L over an alphabet Σ is a subset of the set of all ossible words over Σ, that is $L \subseteq \Sigma^*$.

A finite automaton (FA) is a five-tuple $(Q, \Sigma, q_0, F, \delta)$, here Q is a finite set of states, Σ is an input alphabet, $_0 \in Q$ is the initial state, $F \subseteq Q$ is the set of final states, and is the transition function $\delta: Q \times \Sigma^* \rightarrow Q$. The language ccepted by FA is the set $L(\mathrm{FA}) = \{w \in \Sigma^* | \delta(q_0,w) \in F\}$.

A directed graph (or digraph) G is a pair $G = (V, E)$, V eing a finite, non-empty set of nodes, $E \subseteq V \times V$ being set of edges. A path is a sequence of nodes $v_1, \ldots, v_m$ $n \geqslant 2$) so that $\forall i (1 \leqslant i \leqslant m-1): (v_i,v_{i+1}) \in E$. The mapping $: E \rightarrow X$ is a labelling function, which labels each of the dges in E by a value from the set X.

APPENDIX B. DIFFERENT VERSIONS OF THE ALGEBRA OF TRANSFORMATION

As pointed out in the main text, there is more than one ossibility to define an AT that operates on ECs and RCs. or the sake of easy understanding, the main text describes a ather simple version of an AT whose multistep operation M_M is not commutative, that is, the results of the iterative pplication of M_M partially depend on the order of the EC–EC-constellations to which M_M is applied. The variation hat can occur is a switch between partial ($\mathrm{EC} = P$) and xisting ($\mathrm{EC} = X$) ECs that bear very similar information. lgebra operations delivering results of $\mathrm{EC}_\mathrm{res} = N$, or $\mathrm{EC}_\mathrm{res} = C$, however, are completely unaffected by the order f the integrated ECs and RCs. The switch between partial nd existing ECs is due to the fact that for each step of the lgebra, the previous steps are not taken into account and hat therefore unknown ECs ($\mathrm{EC} = U$) may conceal the prior processing of sub-areas with 'absent' information ($\mathrm{EC} = N$). For example, the sequence $M_\mathrm{M}(M_\mathrm{M}(M_\mathrm{M}(B, S, X), O, P), S, N) = P$ processes such a sub-area at the end and thus correctly delivers $\mathrm{EC}_\mathrm{res} = P$. The sequence $M_\mathrm{M}(M_\mathrm{M}(M_\mathrm{M}(B, S, N), O, P), S, X) = X$, however, processes this sub-area at the beginning and thus results in $\mathrm{EC}_\mathrm{res} = X$ (figure 4 illustrates a similar example).

There are several possibilities to define an algebra for which the multistep operation M_M has commutative properties. For example, it would suffice to replace the unknown EC ($\mathrm{EC} = U$) by two substitutes U_P and U_X, which indicate whether potential resolution of the uncertainty by subsequent algebra operations leads to partial or existing ECs (for example, $M_\mathrm{M}(B, S, N), O, P) = U_\mathrm{P}$, whereas $M_\mathrm{M}(B, O, P), O, P) = U_\mathrm{X}$). This would prevent a switch from partial to existing ECs and render the AT completely independent of the order in which ECs and RCs of a given area constellation are processed.

APPENDIX C. SPECIAL TREATMENT OF EXPLICITLY ABSENT PROJECTIONS

Projections explicitly stated to be absent by tracer investigations are characterized by the injection site showing partial, existing or complete spread of injected tracer substance ($\mathrm{EC} = P, X, C$, respectively), whereas the labelled site shows no transported tracer ($\mathrm{EC} = N$). Note that for anterograde tracing the injected area is identical with the source area, for retrograde tracing with the target area of the projection. If we dealt with absent projections in the same way as with existing ones, certain constellations might lead to the conversion of absent projections into existing ones or vice versa. Envisage, for example, four areas A_1 to A_4 of a map A' and two areas B_1, B_2 of another map B' with A_1, A_2 being sub-areas of B_1 and A_3, A_4 being sub-areas of B_2. If one dealt with the projections $A_1 \xrightarrow{XN} A_3$, $A_1 \xrightarrow{NX} A_4$, $A_2 \xrightarrow{NX} A_3$ and converted the projection from A_1 to A_3 into map B as described for existing projections (see equations (9)–(19)) one would yield a resulting projection code of PrC $(B_1, B_2) = XX$. One straightforward way to prevent such errors is the introduction of three further ECs that do not refer to the existence, but to the non-existence of information. According to the spread of tracer substance in the injected area ($\mathrm{EC} = P, X, C$), these ECs are designated as N_P, N_X, N_C, respectively, and are applied to injection sites only. The AT can then be extended to include these ECs, e.g. $M_\mathrm{M}(C, S, N_\mathrm{P}) = P$, $M_\mathrm{M}(B, O, N_\mathrm{X}) = U$.

APPENDIX D. DEFINITION OF A TRANSFORMATION PATH

A transformation path P is a sequence of at least two areas, each of which has a relation to both its predecessor and successor and all of which are from different maps:

$$P = A_1,A_2, \ldots, A_n (n \geqslant 2) \text{is a transformation path} \Leftrightarrow \forall i,j (1 \leqslant i \leqslant n-1, 1 \leqslant j \leqslant n, i \neq j): (\mathrm{RC}(A_i,A_{i+1}) \in C_\mathrm{RC}) \wedge (A_i \text{ and } A_j \text{ are from different maps}). \quad (A1)$$

A transformation path code C of a given transformation path P is defined as the concatenation of the $n-1$ RCs by which the areas from P are related to each other:

$C(P) = r_1 r_2 \ldots r_{n-1}$
$\mathrm{RC}(A_i, A_{i+1}) = r_i; A_i, A_{i+1}$
are areas in $P; 1 \leqslant i \leqslant n-1$). (A2)

Note that according to this definition RCs are transformation path codes of the length 1.

The resulting relation $\mathrm{RC}_{\mathrm{res}}(P)$ of a transformation path P is defined as the relation that the first area A_1 and the last area A_n of P have on standard cortex: $\mathrm{RC}_{\mathrm{res}}(P) = \mathrm{RC}(A_1, A_n)$. A transformation path P is valid if and only if its sequence of RCs does not account for a possible spatial configuration of the involved areas on standard cortex for which the first and the last area of P are no longer coextensive in some way. The transformation path code $C(P)$ is valid if and only if P is a valid transformation path. Formally:

$\mathrm{RC}_{\mathrm{res}}(P) \neq D \Leftrightarrow P$ is valid $\Leftrightarrow C(P)$ is valid. (A3)

For example, a transformation path in which a sequence of L-relations is followed by a sequence of S-relations is valid because it guarantees overlap of A_1 and A_n (even though the resulting RCs may vary; see figure 6*c*). A path with a reversal of this order, however, allows both overlapping and disjoint positions of A_1 and A_n (see figure 6*a*) and is therefore invalid.

APPENDIX E. DEFINITION OF FORMAL LANGUAGES THAT CHARACTERIZE PATH CATEGORIES

Considering the set C_{RC} as an alphabet, we define the formal language L to contain all possible combinations of non-disjoint RCs with a minimum length of 1 (see appendix A for the definition of the operators $^+$ and *):

$L = C_{\mathrm{RC}}{}^+$. (A4)

L thus comprises all potential transformation path codes and can be further subdivided into subsets L_+ (containing all valid transformation path codes) and L_0 (containing all invalid transformation path codes): $L = L_+ \cup L_0$. Valid transformation paths possess different degrees of potential ambiguity when used by the AT. For example, a mixed sequence of I- and S-relations is unequivocal, whereas a sequence of L-relations may well lead to ambiguities of the AT (see tables 1 and 2). We define subsets L_1 to L_5 of L_+ as path categories whose transformation path codes possess equivalent degrees of ambiguity:

$L_1 = I^+$
$L_2 = (I^* S I^*)^+$
$L_3 = (I^* L I^*)^+$
$L_4 = (I^* L I^*)^+ (I^* S I^*)^+ \cup (I^* L I^*)^+ I^* O I^* (I^* S^* I^*)^*$
$L_5 = I^* O I^*$.

The set L_0 of invalid transformation path codes then simply is the difference between L and L_1–L_5:

$L_0 = L(L_1 \cup L_2 \cup L_3 \cup L_4 \cup L_5)$
$\quad = L \backslash L_+$. (A5)

The indices of L_1–L_5 express a hierarchical order: the lower the index of a path category, the lower the probability that a path from this class may evoke ambiguous constellations for the AT. L_1–L_2 and L_3–L_5 have very similar degrees of potential ambiguity, respectively. Both L_1 and L_2 will never cause ambiguities for the AT; still we ranked L_1 higher since the S-relations of L_2 require multistep operations of the algebra which are computationally more costly than the single-step operations of the I-relations of L_1. The same argument applies to L_3 and L_5 that also show similar degrees of potential ambiguity (compare O- and L-relations in tables 1 and 2). L_4 takes an intermediate position, as a path P with $C(P) \in L_4$ can account for resulting relations $\mathrm{RC}_{\mathrm{res}}(P) = L$, $\mathrm{RC}_{\mathrm{res}}(P) = O$ and also $\mathrm{RC}_{\mathrm{res}}(P) = S$ (see figure 6*c*,*d*). The actual resulting relation of such a transformation path can be derived by an analysis of its context. If P is a transformation path $P = A_1, A_2, \ldots, A_n (n \geqslant 2)$ and $C(P) \in L_4$ then

$\mathrm{RC}_{\mathrm{res}}(P) = L \Leftrightarrow (\exists$ transformation path V such that $V = A_1, \ldots, T$ and $C(V) \in (L_3 \cup L_5), T \neq A_n, T$ being from the same map as $A_n) \wedge \neg(\exists$ transformation path W such that $W = A_n, \ldots, U$ and $C(W) \in L_+$, $U \neq A_1$, U being from the same map as A_1). (A6)

$\mathrm{RC}_{\mathrm{res}}(P) = S \Leftrightarrow (\exists$ transformation path V such that $V = T, \ldots, A_n, C(V) \in (L_2 \cup L_5), T \neq A_1, T$ being from the same map as $A_1) \wedge \neg(\exists$ transformation path W such that $W = U, \ldots, A_1$ and $C(W) \in L_+, U \neq A_n$, U being from the same map as A_n). (A7)

$\mathrm{RC}_{\mathrm{res}}(P) = O \Leftrightarrow (\exists$ transformation path V such that $V = T, \ldots, A_n, C(V) \in (L_2 \cup L_5)$, $T \neq A_1$, T being from the same map as $A_1) \wedge (\exists$ transformation path W such that $W = U, \ldots, A_1$ and $C(W) \in (L_2 \cup L_5)$, $U \neq A_n, U$ being from the same map as $A_n) \wedge \neg$ $(\exists$ transformation path X such that $X = A_1, \ldots, R$ and $C(X) \in (L_1 \cap L_2)$, $R \neq A_n$, R being from the same map as A_n). (A8)

Obviously, this analysis is only possible if there is a sufficient amount of information available on relations between the two maps to which A_1 and A_n belong. This especially concerns the distinction between S- and O-relations that have identical computational properties as they both require the multistep mapping M_{M} of the AT (table 1) by which they are integrated with further overlapping or sub-areas. In contrast to sub-areas, however, there are some constellations for overlapping areas that lead to resulting unknown ECs ($\mathrm{EC}_{\mathrm{res}} = U$). That is, falsely assuming an overlapping area to be a sub-area, one would be at risk to deliver false results. Vice versa, if one falsely assumes a sub-area to be an overlapping area, the worst case is to obtain an unknown EC and thus no result at all (see table 1). If one does not have a database with a sufficiently large amount of information about areal relations, one may therefore pragmatically adopt a 'worst-case behaviour' by treating those paths from L_4 as O-relations whose resulting $\mathrm{RC}_{\mathrm{res}}(P) \neq L$.

Summarizing our descriptions of path categories, the esulting RCs of paths P_1 and P_2 whose transformation ath codes are members of the same path category L_i $1 \leqslant i \leqslant 5$) are as follows:

$$
\begin{aligned}
&'(P_1),\ C(P_2) \in L_1 \Rightarrow \mathrm{RC}_{\mathrm{res}}(P_1) = \mathrm{RC}_{\mathrm{res}}(P_2) = I\\
&'(P_1),\ C(P_2) \in L_2 \Rightarrow \mathrm{RC}_{\mathrm{res}}(P_1) = \mathrm{RC}_{\mathrm{res}}(P_2) = S\\
&'(P_1),\ C(P_2) \in L_3 \Rightarrow \mathrm{RC}_{\mathrm{res}}(P_1) = \mathrm{RC}_{\mathrm{res}}(P_2) = L\\
&'(P_1),\ C(P_2) \in L_4 \Rightarrow \mathrm{RC}_{\mathrm{res}}(P_1),\ \mathrm{RC}_{\mathrm{res}}(P_2) \in \{S,L,O\}\\
&'(P_1),\ C(P_2) \in L_5 \Rightarrow \mathrm{RC}_{\mathrm{res}}(P_1) = \mathrm{RC}_{\mathrm{res}}(P_2) = O. \qquad \text{(A9)}
\end{aligned}
$$

APPENDIX F. DEFINITION OF A FINITE AUTOMATON FOR THE DETECTION OF VALID AND AMBIGUOUS PATHS

After defining path categories as sets of equivalent ransformation paths, we formally define a FA that deter- ines for any given word $w \in L$ which path category it elongs to (see general definition of a FA in Appendix A):

$$
\begin{aligned}
\text{FA} = (\Sigma,Q,q_0,F,\delta) \text{ with } \Sigma &= \{I,S,L,O\} = C_{\mathrm{RC}}\\
Q &= \{\mathrm{START},0,1,2,3,4,5\}\\
q_0 &= \mathrm{START}\\
F &= \{1,2,3,4,5\}\\
\delta: Q \times \Sigma^* &\rightarrow Q \text{ as specified by figure 8.}
\end{aligned}
\qquad \text{(A10)}
$$

he regular language $L(\mathrm{FA})$ that is recognized by FA hen equals the set of all valid transformation path codes:

$$
\begin{aligned}
(\mathrm{FA}) &= \{x \in \Sigma^* | \delta(q_0,x) \in F\}\\
&= L_1 \cup L_2 \cup L_3 \cup L_4 \cup L_5 = L_+. \qquad \text{(A11)}
\end{aligned}
$$

APPENDIX G. DEFINITION OF A TRANSFORMATION GRAPH

Within ORT, a transformation graph is a directed raph with the following special characteristics: the set of odes V is a set of cortical areas from different brain aps, and the set of edges E represents the relations etween these areas. Each path within a transformation raph that does not include any two areas from the same ap meets the conditions of a transformation path (see quation (A1)). The labelling function η: $E \rightarrow L_+$ labels dges with words $w \in L_+$, that is valid transformation ath codes. Note, that $L_+ \supseteq C_{\mathrm{RC}}$ and that thus edges of a ransformation graph can be labelled by both single RCs nd valid combinations thereof.

APPENDIX H. PRINCIPLES OF FLOYD'S ALGORITHM AND DETAILS OF OUR ADAPTATION

Our adaptation of Floyd's algorithm uses a function λ: $\rightarrow \{0, \ldots, 5\}$, which determines the path category of a iven word $w \in L$ by use of the automaton described bove: if $w \in L_i (i \in \{0, \ldots, 5\})$ then $\lambda(w) = i$. Providing hat the initial graph G_0 consists of n nodes $(n \geqslant 1)$, the lgorithm computes a sequence of graphs $G_0, G_1, \ldots, G_n$. At each step, G_i results from modification of $G_{i-1} (1 \leqslant i \leqslant n)$. Each graph G_i is defined as follows:

(i) G_i has the same set of nodes as G_0.
(ii) G_i has an edge (v, w) with $\eta(v, w) = a \Leftrightarrow$. There is a transformation path P from node v to node w in G_0 that includes only nodes of $\{1, \ldots, i\}$ and is represented by the transformation path code $\alpha \in L_+$.

The ith step of the algorithm computes G_i out of G_{i-1} as follows. Let $v_1, \ldots, v_r$ be all predecessors and $w_1, \ldots, w_s$ be all successors of node i in G_{i-1} $(r, s \geqslant 0)$. All pairs (v_j, w_k) are evaluated $(0 \leqslant j \leqslant r,\ 0 \leqslant k \leqslant s)$ to see whether the intermediate node i may be used either to establish a hitherto non-existing edge (v_j, w_k) or to relabel an already existing edge (v_j, w_k). If the sequence v_j, i, w_k is a valid path (i.e. $\lambda(\eta(v_j, i) \bullet \eta(i, w_k)) \neq 0$ and v_j and w_k are from different maps; see equation (A1)) then the following criteria of optimality can be applied.

(i) If there is no edge (v_j, w_k) yet, then insert an edge (v_j, w_k) with $\eta(v_j, w_k) = \eta(v_j, i) \bullet \eta(i, w_k)$.
(ii) If there already is an edge (v_j, w_k) and if $\lambda(\eta(v_j, i) \bullet \eta(i, w_k)) < \lambda(\eta(v_j, w_k))$, then $\eta(v_j, w_k) = \eta(v_j, i) \bullet \eta(i, w_k)$.

In both cases, our algorithm not only stores the new transformation path code $\eta(v_j, i) \bullet \eta(i, w_k)$ by labelling the edge (v_j, w_k), but also stores the transformation path $v_j, \ldots, i, \ldots, w_k$ as such, that is the sequence of areas that is represented by $\eta(v_j, i) \bullet \eta(i, w_k)$. After optimization of the graph is completed, it is possible to look up very quickly for any given pair of areas A, C from different maps:

(i) whether or not there is a path from A to C at all (existence of the edge (A, C) within the graph);
(ii) what the relation between A and C is (resulting RC as indicated by the path category of the transformation path code of the edge (A, C)); and
(iii) which intermediate areas $B_1, \ldots, B_m$ $(m \geqslant 0)$ will be involved in mapping information from A to C (sequence of areas contained by the transformation path that is stored for the edge (A, C)).

APPENDIX I. CODING THE PRECISION OF DATA DESCRIPTION (PD CODES)

The measure of optimality we described for the graph-theoretical optimization is only one among several different possibilities. Depending on the information available, it may have a more or less sophisticated structure. For example, in addition to path categories the decision between alternative paths might also take into account the reliability of information on the involved relations, that is the quality of statements in the literature on relations between areas. Unfortunately, estimating the quality of data as such is highly difficult. It is possible, however, to determine the precision by which data are represented and thus to assess their degree of ambiguity for the reader. We have therefore developed a coding for the precision of data description, the PD codes (see §4). Here we briefly summarize the main principles. For each data modality, a specific set of criteria concerning its representation can be defined. For example, data about a cortical area being (un)labelled by transported tracer substance can be

epresented by textual descriptions, by tables, by drawn igures, by photographs or by a combination of some or all f these. Figures may or may not show clear areal borders, pecific areal names and the exact extent of tracer ubstance. Data on labelled neurons may be of qualitative nominal scale) or quantitative (ordinal or metric scale) ature. Regarding each combination of such criteria as a pecific case, one obtains a set of disjoint classes which can e ordered hierarchically according to their potential egree of ambiguity. By careful operationalization of the pplied criteria, this coding gains high observer-ndependence and reproducibility. PD codes can be used oth within methods such as ORT and for differentiated epresentation of data from the literature in databases uch as CoCoMac-Tracer (see §4).

APPENDIX J. ELIMINATING CONTRADICTORY PATHS AFTER GRAPH-THEORETICAL OPTIMIZATION

This section describes how to systematically scan the utcome of the graph-theoretical optimization for ogically contradictory paths resulting from incompatible nformation on relations between different maps. First, we nvestigate all paths originating from the same area of any iven source map and leading to the same target map. hat is, for each area A being a node of the transformation raph and for each target map B', we look for all paths that riginate in A and lead to different areas $B_1, \ldots, B_p$ ithin B' $(p \geqslant 1)$: $A \xrightarrow{\mathrm{RC}_1} B_1, A \xrightarrow{\mathrm{RC}_2} B_2, \ldots, A \xrightarrow{\mathrm{RC}_p} B_p$. ontradiction occurs if area A is identical with, or a sub-rea of an area B_i ($\mathrm{RC}_i \in \{I, S\}$) and has a further relation $\mathrm{RC}_j \in \{I, S, L, O\}$) with another area B_j of B' $(i, j \leqslant p, i \neq j)$:

$$\exists i,j \in \{1, \ldots, p\}, i \neq j: \\ \mathrm{RC}_i \in \{I, S\} \wedge \mathrm{RC}_j \in C_{\mathrm{RC}}. \qquad \text{(A12)}$$

econd, we investigate all paths originating in the same ource map and leading to the same area of any given arget map. That is, for each area B being a node of the ransformation graph and for each map A', we look for ll paths that originate in areas $A_1, \ldots, A_q$ of A' $(q \geqslant 1)$ nd lead to area B: $A_1 \xrightarrow{\mathrm{RC}} B$, $A_2 \xrightarrow{\mathrm{RC}_2} B, \ldots, A_q \xrightarrow{\mathrm{RC}_1} B$. ontradiction occurs if an area A_i is identical with or ncludes area B ($\mathrm{RC}_i \in \{I, L\}$), and another area A_j of A' as a further relation ($\mathrm{RC}_j \in \{I, S, L, O\}$) with area $(i, j \leqslant q, i \neq j)$:

$$\exists i,j \in \{1, \ldots, q\}, i \neq j: \\ \mathrm{RC}_i \in \{I, L\} \wedge \mathrm{RC}_j \in C_{\mathrm{RC}}. \qquad \text{(A13)}$$

Having found contradictory paths, how can we decide hich is to be preferred? This problem is similar to the ecision between alternative paths during the graph-heoretical optimization (see Appendix H), with the xception that here not only a single path may result from he decision but a group of paths which are intrinsically ompatible. For example, one might face the constellation $\xrightarrow{L} B_1$, $A \xrightarrow{O} B_2$, $A \xrightarrow{I} B_3$. The options in this case would be o either accept the two first paths, which are mutually ompatible, or the last one. In analogy to the decision etween alternative paths within the graph-theoretical ptimization (see Appendix H), one can base such a decision on the path categories and/or consider the reliability of the information about the paths (PD codes, see Appendix I).

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