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# 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. ORT enables 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

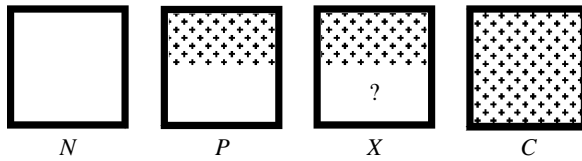


Figure 1. Extension codes (ECs) for the classification of brain data according to the extent that their information is valid for a given cortical area.  $N$ , the information is valid for no part of the area.  $P$ , the information is partially valid for the area.  $X$ , the information exists, i.e.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

have been published before (Stephan & Kötter 1998, 1999), this article is the first complete description of this methodology.

## 2. METHODS

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

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

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

Based on these considerations, one can classify brain data according to the extent to which their information is valid for a specific cortical area  $A$ . We call this classification the extension codes (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  $A$ .

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

It should be noted that this classification is independent of the actual modality of the brain datum, i.e. it can be used to describe both structural (e.g. labelled neurons, transmitter, enzyme or receptor distributions) and functional data (e.g. patterns of activated cortical areas at a given point of time). The actual application of the ECs, however, varies depending on

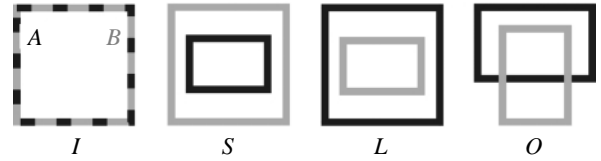


Figure 2. Relation codes (RCs) for the classification of relations between cortical areas from different maps.

$RC(A, B) = I$ :  $A$  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.

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.

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  $EC(B) = P$

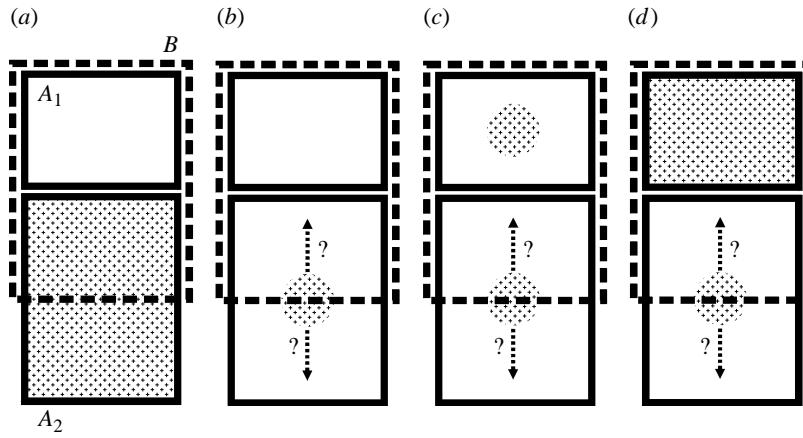


Figure 3. Four examples of simple EC-RC constellations. For all examples  $\text{RC}(A_1, B) = S$ ,  $\text{RC}(A_2, B) = O$ . (a)  $\text{EC}(A_1) = N$ ,  $\text{EC}(A_2) = C$ , resulting  $\text{EC}(B) = P$ . (b)  $\text{EC}(A_1) = N$ ,  $\text{EC}(A_2) = P$ , resulting  $\text{EC}(B) = U$ . (c)  $\text{EC}(A_1) = P$ ,  $\text{EC}(A_2) = P$ , resulting  $\text{EC}(B) = P$ . (d)  $\text{EC}(A_1) = C$ ,  $\text{EC}(A_2) = P$ , resulting  $\text{EC}(B) = X$ .

(figure 3a). If, however,  $A_2$  only carries partial information ( $\text{EC}(A_2) = P$ ), then we cannot decide unambiguously: depending on the exact spatial location of the information (which we do not know), the result for area  $B$  might either be  $\text{EC}(B) = P$  or  $\text{EC}(B) = N$  (figure 3b). This ambiguity is resolved, however, if  $A_1$  carries partial information ( $\text{EC}(A_1) = P$ ) as well (figure 3c). Then the information of  $A_2$  no longer matters (as we will see later, partial information of a sub-area dominates over any other information). It does matter though, if the information contained by  $A_1$  is not partial, but complete ( $\text{EC}(A_1) = C$ ). Then the spatial location and the extent of the information contained by  $A_2$  decides whether  $\text{EC}(B) = P$  or  $\text{EC}(B) = C$ . As we are certain about the validity of the information for  $B$  but cannot determine the extent to which it is valid, this situation is consistent with the above definition of the existing EC, i.e.  $\text{EC}(B) = X$  (figure 3d).

Constellations can become much more complex than these simple examples, though. Furthermore, the amount of data stored by databases is far too large for manual handling and requires automatic, observer-independent processing. Therefore, we have to make the parcellation problem accessible for an algorithmic approach. In other words, we need a formal description for a set of general transformation rules operating on our two sets  $C_{\text{EC}}$  and  $C_{\text{RC}}$ . In computer science, such a construction of several sets and operations is called a ‘heterogeneous algebra’ (Güting 1992). In the following, we will therefore refer to this set of rules as the ‘algebra of transformation’ or simply AT.

For sub- and overlapping areas, the general principle of our AT is as follows: imagine we intend to convert information about an area  $A$  from map  $A'$  to map  $B'$ . First, we have to find all areas  $B_1, \dots, B_m$  ( $m \geq 1$ ) in map  $B'$  that are coextensive in some way with area  $A$  on standard cortex and thus are the target areas of the mapping process. Then, for each area  $B_k$  ( $1 \leq k \leq m$ ), we have to determine all areas  $A_1, \dots, A_n$  ( $n \geq 1$ ) in map  $A'$  which, together with  $A$ , are coextensive in some way with area  $B_k$ . We decide step-by-step how the information of each of the areas  $A_1, \dots, A_n$  is converted to area  $B_k$ . At each step we first consider what we know about the information of  $B_k$  so far. We call this result of previous transformations  $\text{EC}_{\text{prev}}(B_k)$ . Then we turn to the currently processed area  $A_i$  ( $1 \leq i \leq n$ ) of map  $A'$ , determine its relation to  $B_k$  (i.e.  $\text{RC}(A_i, B_k)$ ) and its information (i.e.  $\text{EC}(A_i)$ ) and use the appropriate rule (see table 1) for the triplet  $(\text{EC}_{\text{prev}}(B_k), \text{RC}(A_i, B_k), \text{EC}(A_i))$ . The transformation rule delivers a temporarily resulting EC for  $B_k$ , which

we call  $\text{EC}_{\text{res}}(B_k)$ . This  $\text{EC}_{\text{res}}(B_k)$  serves as input (i.e. as  $\text{EC}_{\text{prev}}(B_k)$ ) for the next step. Having completed the procedure for all areas  $A_1, \dots, A_n$ , we get the final  $\text{EC}_{\text{res}}(B_k)$ . For the moment, we will refrain from discussing whether the order in which  $A_1, \dots, A_n$  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.  $\text{RC}(A, B) = L$  or  $\text{RC}(A, B) = I$ ), 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  $\text{EC}_{\text{prev}}$  above. Instead, all we need to know in this case is the relation between the two areas (i.e.  $\text{RC}(A, B)$ ) and the information about area  $A$  (i.e.  $\text{EC}(A)$ ). 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

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

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

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

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  $EC_{res}(B)$ .)

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

view, therefore, the procedure described above is not 'well defined'. Slight modifications of the simple AT described here, however, are sufficient to render the operation  $M_M$  commutative and 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  $EC_{res}(B)$ .)

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

### (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  $A \cap B \neq \emptyset$ . 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:

$$\begin{aligned} A' &= \{A_1, A_2, \dots, A_a\}, a \geq 1 \\ B' &= \{B_1, B_2, \dots, B_b\}, b \geq 1. \end{aligned} \quad (3)$$

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

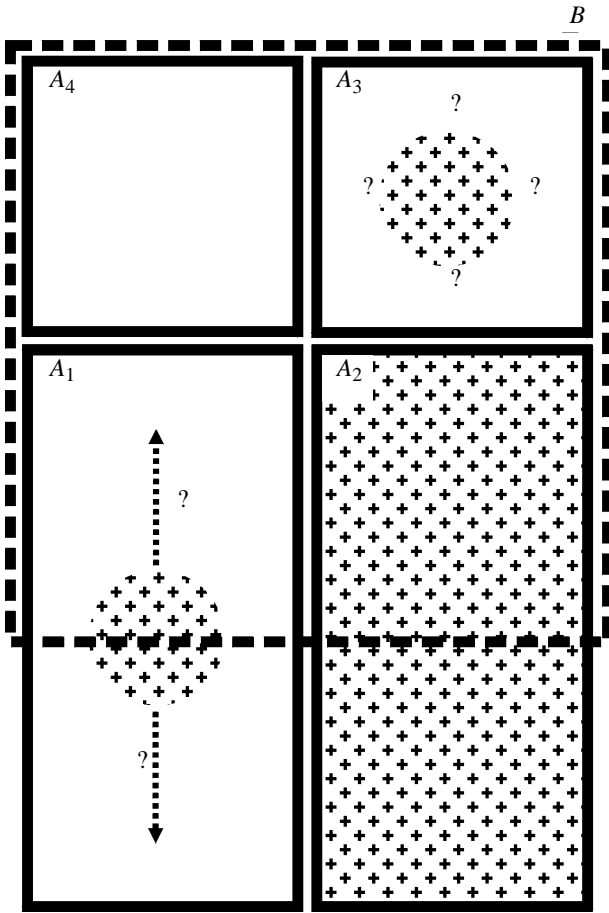


Figure 4. A simple example for the use of the multistep operation  $M_M$  in a transformation process. Relations between areas  $A_1$  to  $A_4$  and  $B$  are  $\text{RC}(A_1, B) = \text{RC}(A_2, B) = O$ ,  $\text{RC}(A_3, B) = \text{RC}(A_4, B) = S$ . Information contained by  $A_1$  to  $A_4$  is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

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

$$\Phi_B = \{B_k \in B' | B_k \cap A_\alpha \neq \emptyset, 1 \leq k \leq b\}. \quad (4)$$

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

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

Please note that  $\Phi_A^k$  is always defined with reference to the  $B_k$  for which the transformation is currently performed. Due to its definition and that of  $\Phi_B$ ,  $\Phi_A^k$  at least contains  $A_\alpha$ .

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

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

$\Phi_A^k$  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  $A_{i_x}$  ( $1 \leq x \leq n$ ) necessarily contributes to the information that  $B_k$  will have as the result of the transformation:

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

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

If  $\text{RC}(A_\alpha, B_k) = I$ , then

$$|\Phi_B| = 1, |\Phi_A^k| = 1, \quad \text{EC}_{\text{res}} = M_S(I, \text{EC}(A_\alpha)). \quad (8a)$$

If  $\text{RC}(A_\alpha, B_k) = L$ , then

$$|\Phi_B| > 1, |\Phi_A^k| = 1, \quad \text{EC}_{\text{res}} = M_S(L, \text{EC}(A_\alpha)). \quad (8b)$$

If the initial area  $A_\alpha$  is a sub-area of or overlapping with  $B_k$ , then  $\Phi_A^k$  has more elements than just  $A_\alpha$ . 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,  $\text{RC}_{i_x}$  and  $\text{EC}_{i_x}$  are used synonymously for  $\text{RC}(A_{i_x}, B_k)$  and  $\text{EC}(A_{i_x})$ , respectively).

If  $\text{RC}(A_\alpha, B_k) = S$ , then

$$|\Phi_B| = 1, |\Phi_A^k| > 1, \quad \text{EC}_{\text{res}} = M_M(\dots M_M(M_M(B, \text{RC}_{i_1}, \text{EC}_{i_1}), \text{RC}_{i_2}, \text{EC}_{i_2}) \dots), \text{RC}_{i_n}, \text{EC}_{i_n}). \quad (8c)$$

If  $\text{RC}(A_\alpha, B_k) = O$ , then

$$|\Phi_B| > 1, |\Phi_A^k| > 1, \quad \text{EC}_{\text{res}} = M_M(\dots M_M(M_M(B, \text{RC}_{i_1}, \text{EC}_{i_1}), \text{RC}_{i_2}, \text{EC}_{i_2}) \dots), \text{RC}_{i_n}, \text{EC}_{i_n}). \quad (8d)$$

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

can be adapted to this specific class of brain data. Transforming connectivity data requires specific considerations for the simple reason that we do not deal only with a source map and target map between which transformation takes place, but every projection also consists of a source and a target area. Their information must be transformed separately while nevertheless considering their mutual context. In essence, there are three main points.

First, the principles of transformation outlined above have to be applied to both the source and target area. The resulting ECs can then be put together to yield a so-called projection code (PrC). However, the ECs of the injected site and of the labelled site (anterograde tracer: injection in the source area of the projection, label in the target area of the projection; retrograde tracer: vice versa) bear slightly different meanings. The EC of the injected site describes only the spread of injected tracer substance and does not state which proportion of somata–terminals from the injected site actually take up and transport tracer substance to the labelled area. On the contrary, the EC of the labelled site describes the actual extent of somata–terminals within the labelled area that receive association fibres from the injected site. Furthermore, many tracer studies have demonstrated that association fibres from an area  $A$  to another area  $B$  often do not originate throughout the whole extent of  $A$  (for example, see Bates & Goldman-Rakic 1993; Luppino *et al.* 1993). This means that injections of different extent and position within the injected site may lead to different and seemingly contradictory ECs of the labelled site. For example, a partial injection of anterograde tracer into area  $A$  might fail to produce label in area  $B$ . However, this does not preclude that a partial anterograde injection into another subpart of  $A$  or a complete anterograde injection into area  $A$  might lead to labelling of area  $B$ . In large databases comprising many different studies, such difficulties can be overcome by data-mining methods in combination with ORT. Although a detailed description of such methods is beyond the limits of this article, one option is to analyse redundant reports on both antero- and retrogradely traced projections. Such an approach has been implemented in the database CoCoMac-Tracer (see §4).

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

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

Assume that we intend to transform the projection

$$P_\alpha: A_p \xrightarrow{\text{EC}(A_p)\text{EC}(A_q)} A_q (1 \leq p, q \leq a) \quad (9)$$

from map  $A'$  to map  $B'$ . Dealing with the transformation of the information of the source area  $A_p$  first, we have

$$\sum_B = \{B_s \in B' | B_s \cap A_p \neq \emptyset, 1 \leq s \leq b\} \quad (10)$$

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

$$\sum_A^s = \{A_f \in A' | A_f \cap B_s \neq \emptyset, 1 \leq f \leq a\} \quad (11)$$

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),  $\sum_A^s$  is always defined with reference to the area  $B_s$  for which the transformation is currently performed. Due to its definition and that of  $\Sigma_B$ ,  $\sum_A^s$  at least contains  $A_p$ .

In correspondence with equation (6), we now determine the index set  $\Gamma^n$  for the areas of  $\sum_A^s$ :

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

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

$$\Omega_1: A_{i_1} \rightarrow A_q, \dots, \Omega_n: A_{i_n} \rightarrow A_q. \quad (13)$$

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

We proceed correspondingly for the target area  $A_q$  of our projection  $P_\alpha$ :

$$T_B = \{B_t \in B' | B_t \cap A_q \neq \emptyset, 1 \leq t \leq b\}, \quad (14)$$

$$T_A^t = \{A_g \in A' | A_g \cap B_t \neq \emptyset, 1 \leq g \leq a\}, \quad (15)$$

$$\Gamma^t = \left\{ j_1, j_2, \dots, j_m | (A_{j_1} \in T_A^t, \dots, A_{j_m} \in T_A^t) \wedge \left( \bigcup_{j=1}^m A_{j_j} = T_A^t \right) \right\} \subseteq \{1, 2, \dots, a\}. \quad (16)$$

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

$$\Psi_1: A_p \rightarrow A_{j_1}, \dots, \Psi_m: A_p \rightarrow A_{j_m}. \quad (17)$$

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

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  $\Sigma_B \times T_B$ :

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

The set  $\Theta(P_\alpha)$  comprises all projections in map  $B'$  which result from the transformation of the projection  $P_\alpha$  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  $\bullet$ ):

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

### (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

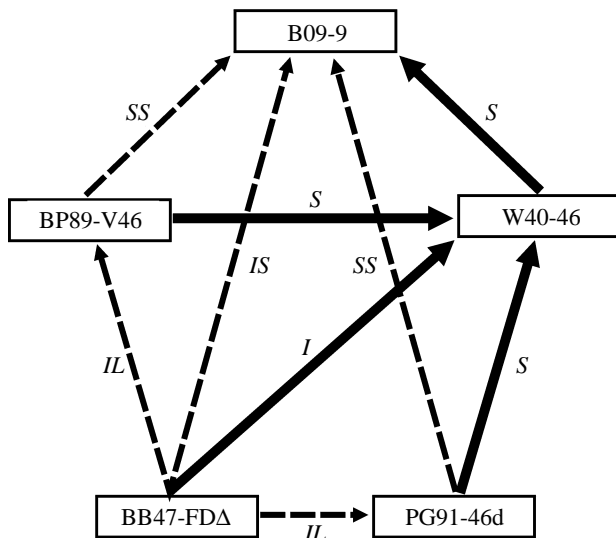


Figure 5. A simple example of a transformation graph consisting of five areas. Abbreviations are as follows: B09-9, area 9 of Brodmann (1909); BB47-FDA, area FDA of von Bonin & Bailey (1947); BP89-V46, area V46 of Barbas & Pandya (1989); PG91-46d, area 46d of Preuss & Goldman-Rakic (1991a); and W40-46, area 46 of Walker (1940). Edges are represented by bold and broken arrows. Bold arrows designate initially known relations between areas, broken arrows show initially unknown relations that are deduced by graph-theoretical optimisation. Labels of arrows designate the transformation path codes. Note that for each pair of related areas, this figure shows only one relation—arrow; the reverse relations—arrows have been left out to maintain clarity of the diagram.

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

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

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

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

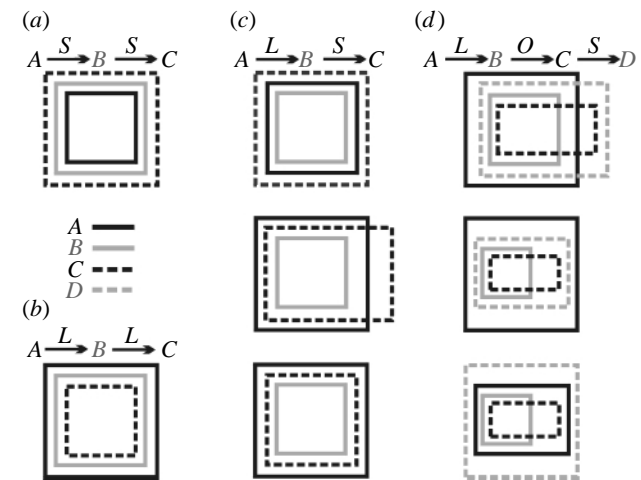


Figure 6. Examples of valid transformation paths.

(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 ( $RC_{res}(A, C) = S/O/L$ ).

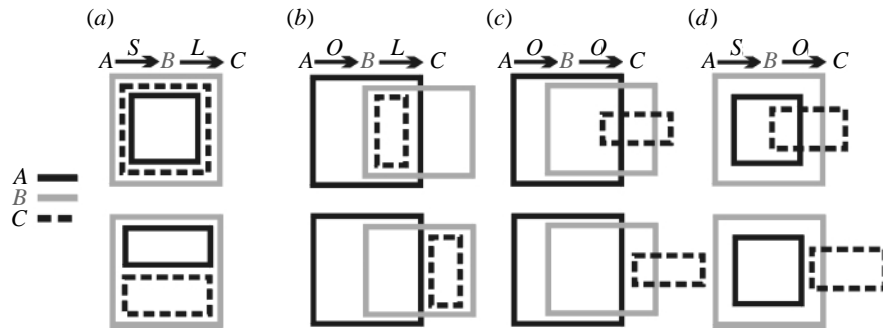
(d) Three paths, each represented by the transformation path code  $LOS$  (path category  $L_4$ ), demonstrate that the additional occurrence of a single  $O$ -relation between sequences of  $L$ - and  $S$ -relations still maintains validity and yields the same three different resulting RCs as for (c).

- (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  $B_1, \dots, B_n$  of  $n$  different maps ( $n \geq 1$ ). 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 7c). In addition to this case, there are some further constellations that also lead to ambiguous results (figure 7 illustrates this schematically).



Figures 7. Examples of invalid transformation paths (path category  $L_0$ ). For each of the paths (a)–(d) the upper row shows possible spatial configurations of the involved areas for which some coextension of the first and last area is present. The lower row demonstrates that the areas of the same path may have relative positions for which the first and last area are no longer coextensive 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  $L$  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 1). 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 F for the exact definitions).

### (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 ( $n \geq 1$ ) 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  $G_0, G_1, \dots, G_n$  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

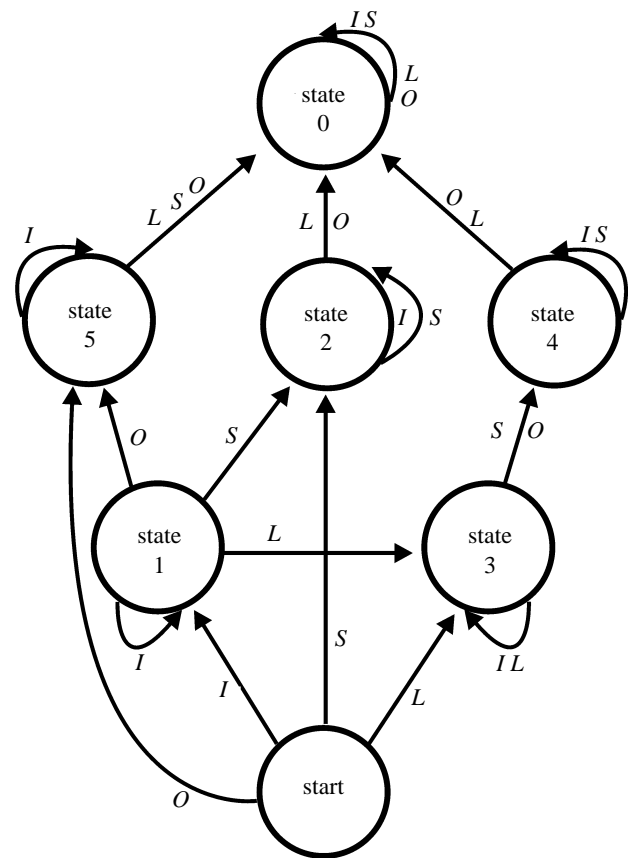


Figure 8. A finite automaton for the detection of valid and ambiguous transformation paths. Beginning at state 'START', the automaton reads a given word  $w \in L$  representing a transformation path. Each RC evokes changes of state as indicated by the labels of the arrows. The index of the state in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

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  $v_j$  ( $j \geq 0$ ) and successors  $w_k$  ( $k \geq 0$ ) 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

areas  $v_j, \dots, i, \dots, w_k$  by which the nodes  $v_j$  and  $w_k$  are connected (using this sequence, the AT can later transform information from area  $v_j$  to area  $w_k$  via the intermediate areas). After  $n$  steps, the optimized transformation graph  $G_n$  is produced, which contains all valid transformation paths with a minimal potential of ambiguity (see Appendix H and the example in figure 5).

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

### 3. PRACTICAL BENEFITS OF ORT: TWO EXAMPLES

Having described the theoretical principles of ORT, we demonstrate its practical benefits with the help of two examples. These examples are of complementary character by illustrating how (i) the same data set can be transformed to different parcellation schemes, and how vice versa (ii) different data sets can be transformed to the same parcellation scheme.

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

First, we show how ORT can be used for differentiation and control of analyses by juxtaposing results from an analytical study on the functional connectivity of primate cerebral cortex (Stephan *et al.*, this issue). Using three independent methods of analysis, this study demonstrated the highly clustered structure of the functional cortical network. The analyses were based on the database CoCoMac-Stry, which contains data on functional connectivity in macaque cortex (see §4). With the help of ORT, the original data were transformed to two different parcellation schemes: one was the less-known parcellation of McCulloch (1944), the other one was a 'hybrid map' composed of the well-known and still widely used parcellations of Walker (1940) for the prefrontal cortex and von Bonin & Bailey (1947) for the rest of the cortex. For convenience, we here designate these two data sets as the '*M*-data' (McCulloch) and '*H*-data' (hybrid), respectively. Exactly the same analyses were applied to both data sets. While Stephan *et al.* (this issue) presented only the results from the *H*-data, we here directly juxtapose results from balanced optimal set analysis (OSA; see Hilgetag *et al.* 1998; Hilgetag, Burns, O'Neill, Scannell & Young, this issue, for details) on binarily classified data. The comparison of the two resulting clusterplots (figure 9*a,b*) reveals that, while the results were generally compatible, each data set offered slightly different perspectives. Both figures clearly show the principal clusters of the functional network that constantly emerged from all analyses performed by this study: orbitofronto-temporal, visual and somatomotor clusters. Without going into detail, it is apparent, however, that the intrinsic composition of these clusters showed variations between the two data sets (compare figure 9*a* and *b*). For example, the visual cluster, which 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 relations 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 transformation-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 transformation 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 somatomotor 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 anatomically, 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 situation. 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.

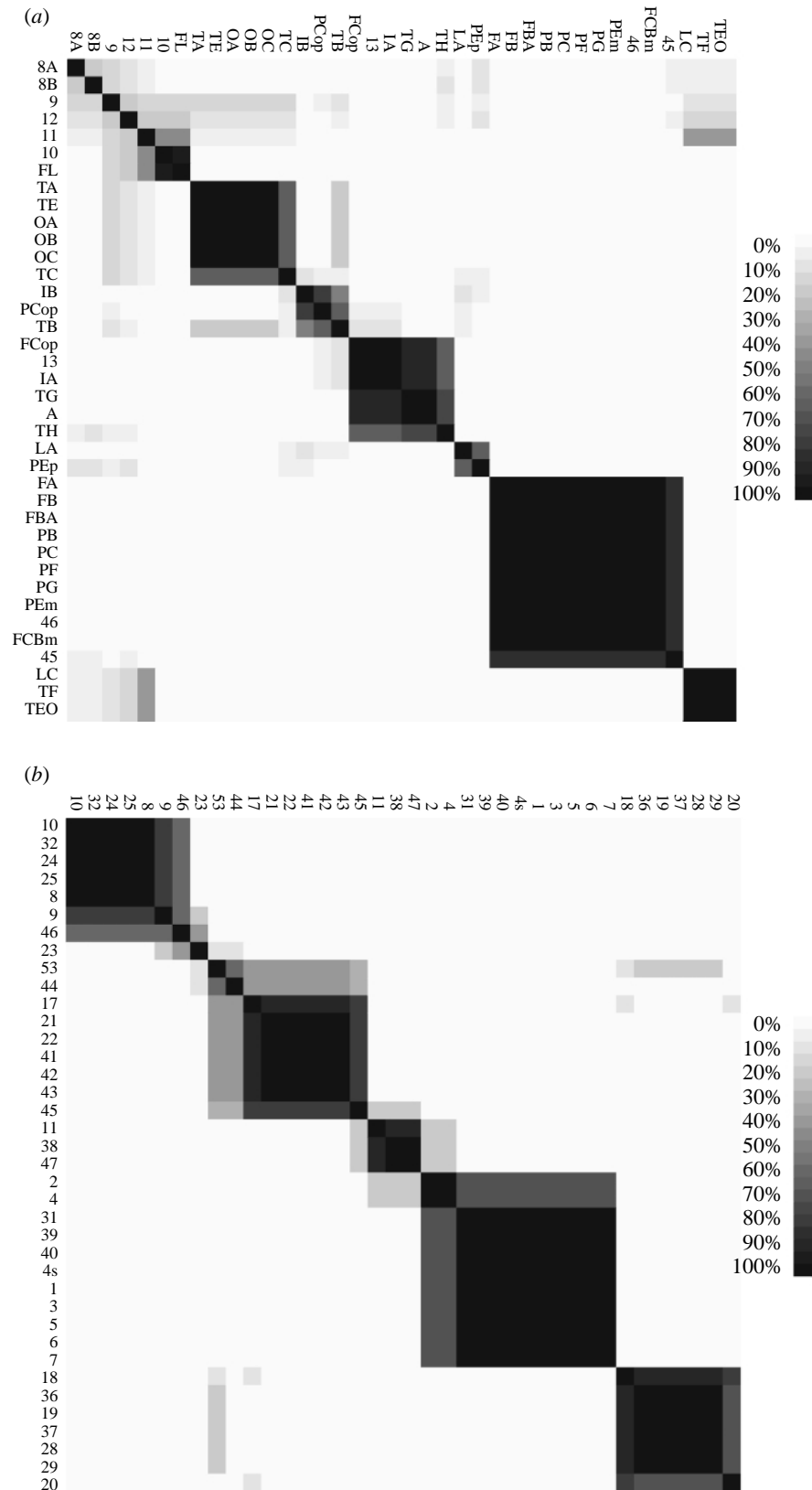


Figure 9. Two clusterplots resulting from optimal set analysis (OSA; see Hilgetag, Burns, O'Neill, Scannell & Young, this issue, for details) under balanced conditions for the same data set (binarily classified data on functional connectivity in macaque cerebral cortex; see Stephan *et al.*, this issue, 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	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0
FB	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FBA	1	1	1	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0
FCBm	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
46	0	1	1	1	1	0	0	0	0	0	1	1	1	1	1	1	0	0
PB	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
PC	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PEm	0	1	0	0	0	0	0	1	0	1	1	1	0	0	0	1	0	0
PEp	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	1	0	1
PF	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
PG	0	0	0	0	1	0	1	1	0	0	0	1	1	0	1	0	1	1
TA	0	0	0	0	1	0	1	0	0	1	0	1	1	1	1	1	0	0
TE	0	0	0	0	1	0	0	0	0	1	0	0	1	1	0	1	1	1
TEO	0	0	0	0	1	0	0	0	0	1	1	1	1	0	1	1	1	1
TF	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	1	1	1
OA	0	0	0	0	1	0	1	1	0	1	1	1	1	1	0	0	1	1
OB	0	0	0	0	0	0	1	1	0	0	1	0	1	0	1	0	1	1
OC	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	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	0	0	1	1	1	1	1	0	0	1	0	1	1	0
FB	1	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0
FBA	1	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	0	0
FCBm	1	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	0	0
46	0	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	0	0
PB	1	0	1	1	0	1	1	0	1	1	1	1	0	0	0	0	0	0
PC	1	1	1	1	0	0	1	1	1	1	1	0	0	0	0	0	0	0
PEm	1	1	0	0	1	0	1	0	1	1	1	1	1	1	1	1	1	1
PEp	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1	1
PF	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1	1	1	1
PG	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1	1	1	1
TA	0	0	0	0	1	0	0	0	1	0	0	1	1	1	1	1	1	1
TE	0	0	0	0	1	0	0	1	1	1	1	1	0	1	1	1	1	1
TEO	0	0	0	0	1	0	0	1	0	1	0	1	1	0	1	1	1	0
TF	0	0	0	0	1	0	0	0	0	1	0	1	1	1	0	1	0	0
OA	0	0	0	0	1	0	1	0	1	1	1	1	1	1	0	0	1	1
OB	0	0	0	0	0	0	0	0	0	1	0	1	0	1	1	1	1	1
OC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1

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

#### 4. DISCUSSION

ORT is a simple, yet effective method by which the large amount of already published data can be trans-

formed 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 cytoarchitecturally 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

what way, are explicitly represented, thus the mapping process is fully transparent.

Coordinate-independence is not only responsible for potential problems of ambiguity, but also affords important advantages of ORT. It accounts for the relatively simple, yet effective, principles of ORT that can easily be incorporated in algorithms within neuroscientific database systems (see below). Most importantly, coordinate-independence ensures that ORT makes very few demands on the data it transforms. All it requires is that they are described on the basis of a known parcellation scheme. Only in this way can the huge amount of data from already published studies (e.g. tracer studies) be made accessible and comparable by their organization in powerful databases.

Another question that should be addressed is whether ORT is equally suitable for different modalities of brain data. ORT, as it is described here, is primarily designed for brain data of binary nature on a nominal scale (e.g. existence or non-existence of transported tracer substance in a given area). For such data, the necessary algebra of transformation is relatively simple to define (see tables 1 and 2). It becomes more complicated if dealing with data that are still on a nominal scale but show more than two disjoint classes (e.g. laminar patterns of transported tracer substance). These cases can still be coped with by extending the operations of the algebra to include an additional factor (e.g. a code for the laminar pattern), thus accounting for the special properties of the transformed data. In this way, the algebra operations do not only deliver a resulting EC but also specify how the information as such is affected by the transformation. Other data types that are measured on metric scales, such as quantitative measurements of enzyme or receptor densities, however, seem to be beyond the scope of ORT. Although scale transformations may prove useful for such conditions (e.g. transferring metric data to a nominal scale by applying an appropriate threshold), a large proportion of the original information would be lost. Therefore, metric data require absolute spatial reference systems because the degree of spatial overlap quantitatively determines the outcome of the transformation.

Currently available spatial methods of mapping brain data 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 more recent approaches is the intersubject spatial variability of the human brain. The classical brain maps from the beginning of the 20th century were based on the analysis of one or a few brains, and the maps were presented as schematic drawings. Thus, such maps cannot be used for spatial mapping purposes and do not reflect intersubject variability. However, even if the mapping is performed by a real three-dimensional representation of data, the problem of intersubject anatomical variability must be solved. This is presently done by the development of techniques that allow the linear and/or nonlinear deformation of the three-dimensional data set of an individual brain into a spatial reference system, e.g. an individual 'standard' brain or an 'average' brain constructed from a large sample of individual brains. Presently, these spatial 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 of Hopcroft & Ullman (1979), Güting (1992) and Rozenberg & Salooma (1997) for formal languages, finite automata and graphs. We here give a brief summary of some definitions which are fundamental for an understanding of this appendix.

An alphabet  $\Sigma$  is a finite, non-empty set. The elements of an alphabet  $\Sigma$  are called letters or symbols. A word over an alphabet  $\Sigma$  is a finite sequence of  $n$  letters ( $n \geq 0$ ), including the empty word  $\varepsilon$ . Note that according to this definition, letters are words of the length 1. If  $x = x_1 x_2 \dots x_n$  and  $y = y_1 y_2 \dots y_m$  ( $n, m \geq 0$ ) are words over an alphabet  $\Sigma$ , so is their concatenation  $x \bullet y$  (or simply  $xy$ ) obtained by writing  $x$  and  $y$  one after another:  $x \bullet y = xy = x_1 x_2 \dots x_n y_1 y_2 \dots y_m$ . For a given alphabet  $\Sigma$ , the set of all possible words over  $\Sigma$  (including the empty word  $\varepsilon$ ) is defined as  $\Sigma^*$  and the set of all non-empty words over  $\Sigma$  as  $\Sigma^+ = \Sigma^* \setminus \{\varepsilon\}$ . Observe that  $\Sigma^*$  and  $\Sigma^+$  are always infinite. A (formal) language  $L$  over an alphabet  $\Sigma$  is a subset of the set of all possible words over  $\Sigma$ , that is  $L \subseteq \Sigma^*$ .

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

A directed graph (or digraph)  $G$  is a pair  $G = (V, E)$ ,  $V$  being a finite, non-empty set of nodes,  $E \subseteq V \times V$  being a set of edges. A path is a sequence of nodes  $v_1, \dots, v_m$  ( $m \geq 2$ ) so that  $\forall i(1 \leq i \leq m-1): (v_i, v_{i+1}) \in E$ . The mapping  $\eta: E \rightarrow X$  is a labelling function, which labels each of the edges 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 possibility to define an AT that operates on ECs and RCs. For the sake of easy understanding, the main text describes a rather simple version of an AT whose multistep operation  $M_M$  is not commutative, that is, the results of the iterative application of  $M_M$  partially depend on the order of the EC–RC-constellations to which  $M_M$  is applied. The variation that can occur is a switch between partial ( $\text{EC} = P$ ) and existing ( $\text{EC} = X$ ) ECs that bear very similar information. Algebra operations delivering results of  $\text{EC}_{\text{res}} = \mathcal{N}$ , or  $\text{EC}_{\text{res}} = C$ , however, are completely unaffected by the order of the integrated ECs and RCs. The switch between partial and existing ECs is due to the fact that for each step of the algebra, the previous steps are not taken into account and that therefore unknown ECs ( $\text{EC} = U$ ) may conceal the

prior processing of sub-areas with 'absent' information ( $\text{EC} = \mathcal{N}$ ). For example, the sequence  $M_M(M_M(M_M(B, S, X), O, P), S, \mathcal{N}) = P$  processes such a sub-area at the end and thus correctly delivers  $\text{EC}_{\text{res}} = P$ . The sequence  $M_M(M_M(M_M(B, S, \mathcal{N}), O, P), S, X) = X$ , however, processes this sub-area at the beginning and thus results in  $\text{EC}_{\text{res}} = X$  (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 ( $\text{EC} = U$ ) 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,  $M_M(B, S, \mathcal{N}), O, P) = U_P$ , whereas  $M_M(B, O, P), O, P) = U_X$ ). 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 ( $\text{EC} = P, X, C$ , respectively), whereas the labelled site shows no transported tracer ( $\text{EC} = \mathcal{N}$ ). 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  $A_1 \xrightarrow{XV} A_3, A_1 \xrightarrow{MX} A_4, A_2 \xrightarrow{NX} A_3$  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  $\text{PrC}(B_1, B_2) = XX$ . 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 ( $\text{EC} = P, X, C$ ), these ECs are designated as  $\mathcal{N}_P, \mathcal{N}_X, \mathcal{N}_C$ , respectively, and are applied to injection sites only. The AT can then be extended to include these ECs, e.g.  $M_M(C, S, \mathcal{N}_P) = P, M_M(B, O, \mathcal{N}_X) = U$ .

## 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:

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

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:

$$\begin{aligned}
C(P) &= r_1 r_2 \dots r_{n-1} \\
(\text{RC}(A_i, A_{i+1}) &= r_i; A_i, A_{i+1} \\
\text{are areas in } P; 1 &\leq i \leq n-1).
\end{aligned} \tag{A2}$$

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

The resulting relation  $\text{RC}_{\text{res}}(P)$  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:  $\text{RC}_{\text{res}}(P) = \text{RC}(A_1, A_n)$ . 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:

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

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 6c). A path with a reversal of this order, however, allows both overlapping and disjoint positions of  $A_1$  and  $A_n$  (see figure 7a) and is therefore invalid.

#### APPENDIX E. DEFINITION OF FORMAL LANGUAGES THAT CHARACTERIZE PATH CATEGORIES

Considering the set  $C_{\text{RC}}$  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  $^*$ ):

$$L = C_{\text{RC}}^+. \tag{A4}$$

$L$  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:

$$\begin{aligned}
L_1 &= I^+ \\
L_2 &= (I^* S I^*)^+ \\
L_3 &= (I^* L I^*)^+ \\
L_4 &= (I^* L I^*)^+ (I^* S I^*)^+ \cup (I^* L I^*)^+ I^* O I^* (I^* S^* I^*)^* \\
L_5 &= I^* O I^*.
\end{aligned}$$

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

$$\begin{aligned}
L_0 &= L(L_1 \cup L_2 \cup L_3 \cup L_4 \cup L_5) \\
&= L \setminus L_+.
\end{aligned} \tag{A5}$$

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  $\text{RC}_{\text{res}}(P) = L$ ,  $\text{RC}_{\text{res}}(P) = O$  and also  $\text{RC}_{\text{res}}(P) = S$  (see figure 6c,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  $P = A_1, A_2, \dots, A_n (n \geq 2)$  and  $C(P) \in L_4$  then

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

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

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

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 ( $\text{EC}_{\text{res}} = U$ ). 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  $\text{RC}_{\text{res}}(P) \neq L$ .

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

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

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

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

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

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

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

## APPENDIX G. DEFINITION OF A TRANSFORMATION GRAPH

Within ORT, a transformation graph is a directed graph with the following special characteristics: the set of nodes  $V$  is a set of cortical areas from different brain maps, and the set of edges  $E$  represents the relations between these areas. Each path within a transformation graph that does not include any two areas from the same map meets the conditions of a transformation path (see equation (A1)). The labelling function  $\eta: E \rightarrow L_+$  labels edges with words  $w \in L_+$ , that is valid transformation path codes. Note, that  $L_+ \supseteq C_{\text{RC}}$  and that thus edges of a transformation graph can be labelled by both single RCs and valid combinations thereof.

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

Our adaptation of Floyd's algorithm uses a function  $\lambda: L \rightarrow \{0, \dots, 5\}$ , which determines the path category of a given word  $w \in L$  by use of the automaton described above: if  $w \in L_i$  ( $i \in \{0, \dots, 5\}$ ) then  $\lambda(w) = i$ . Providing that the initial graph  $G_0$  consists of  $n$  nodes ( $n \geq 1$ ), the algorithm computes a sequence of graphs  $G_0, G_1, \dots, G_n$ .

At each step,  $G_i$  results from modification of  $G_{i-1}$  ( $1 \leq i \leq n$ ). 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  $\{1, \dots, i\}$  and is represented by the transformation path code  $\alpha \in L_+$ .

The  $i$ th step of the algorithm computes  $G_i$  out of  $G_{i-1}$  as follows. Let  $v_1, \dots, v_r$  be all predecessors and  $w_1, \dots, w_s$  be all successors of node  $i$  in  $G_{i-1}$  ( $r, s \geq 0$ ). All pairs  $(v_j, w_k)$  are evaluated ( $0 \leq j \leq r, 0 \leq k \leq s$ ) 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  $v_j, \dots, i, \dots, w_k$  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  $B_1, \dots, B_m$  ( $m \geq 0$ ) 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

represented by textual descriptions, by tables, by drawn figures, by photographs or by a combination of some or all of these. Figures may or may not show clear areal borders, specific areal names and the exact extent of tracer substance. Data on labelled neurons may be of qualitative (nominal scale) or quantitative (ordinal or metric scale) nature. Regarding each combination of such criteria as a specific case, one obtains a set of disjoint classes which can be ordered hierarchically according to their potential degree of ambiguity. By careful operationalization of the applied criteria, this coding gains high observer-independence and reproducibility. PD codes can be used both within methods such as ORT and for differentiated representation of data from the literature in databases such as CoCoMac-Tracer (see §4).

#### APPENDIX J. ELIMINATING CONTRADICTIONARY PATHS AFTER GRAPH-THEORETICAL OPTIMIZATION

This section describes how to systematically scan the outcome of the graph-theoretical optimization for logically contradictory paths resulting from incompatible information on relations between different maps. First, we investigate all paths originating from the same area of any given source map and leading to the same target map. That is, for each area  $A$  being a node of the transformation graph and for each target map  $B'$ , we look for all paths that originate in  $A$  and lead to different areas  $B_1, \dots, B_p$  within  $B'$  ( $p \geq 1$ ):  $A \xrightarrow{RC_1} B_1, A \xrightarrow{RC_2} B_2, \dots, A \xrightarrow{RC_p} B_p$ . Contradiction occurs if area  $A$  is identical with, or a sub-area of an area  $B_i$  ( $RC_i \in \{I, S\}$ ) and has a further relation ( $RC_j \in \{I, S, L, O\}$ ) with another area  $B_j$  of  $B'$  ( $i, j \leq p, i \neq j$ ):

$$\exists i, j \in \{1, \dots, p\}, i \neq j: \\ RC_i \in \{I, S\} \wedge RC_j \in C_{RC}. \quad (A12)$$

Second, we investigate all paths originating in the same source map and leading to the same area of any given target map. That is, for each area  $B$  being a node of the transformation graph and for each map  $A'$ , we look for all paths that originate in areas  $A_1, \dots, A_q$  of  $A'$  ( $q \geq 1$ ) and lead to area  $B$ :  $A_1 \xrightarrow{RC} B, A_2 \xrightarrow{RC} B, \dots, A_q \xrightarrow{RC} B$ . Contradiction occurs if an area  $A_i$  is identical with or includes area  $B$  ( $RC_i \in \{I, L\}$ ), and another area  $A_j$  of  $A'$  has a further relation ( $RC_j \in \{I, S, L, O\}$ ) with area  $B$  ( $i, j \leq q, i \neq j$ ):

$$\exists i, j \in \{1, \dots, q\}, i \neq j: \\ RC_i \in \{I, L\} \wedge RC_j \in C_{RC}. \quad (A13)$$

Having found contradictory paths, how can we decide which is to be preferred? This problem is similar to the decision between alternative paths during the graph-theoretical optimization (see Appendix H), with the exception that here not only a single path may result from the decision but a group of paths which are intrinsically compatible. For example, one might face the constellation  $A \xrightarrow{L} B_1, A \xrightarrow{O} B_2, A \xrightarrow{I} B_3$ . The options in this case would be to either accept the two first paths, which are mutually compatible, or the last one. In analogy to the decision between alternative paths within the graph-theoretical optimization (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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