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Structural modeling of functional neural pathways mapped with 2-deoxyglucose: effects of acoustic startle habituation on the auditory system

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This paper describes the first application of structural modeling to neuroscience. Structural modeling (also known as path analysis) is a method to assess the relative impact of directional links in a system and how these interrelations may change under different conditions. The objective was to demonstrate how structural modeling can be used to determine the functional interrelationships between brain structures that form the auditory system. Using structural modeling, changes in auditory system 2-DG uptake were examined during long- and short-term habituation of the acoustic startle reflex. Models were based on the anatomical connections between central auditory system structures. Using functional 2-DG data, the correlations between these structures were calculated and numerical weights were computed for each anatomical link. The analysis revealed that the lemniscal path was dominant during short-term habituation, while during long-term habituation this influence was modified through extra-lemniscal pathways. The models are discussed in the context of previous findings to demonstrate how structural modeling can not only complement, but also extract more information from 2-DG mapping experiments.

INTRODUCTION

A method which allows for the assessment of the changes in entire systems is structural modeling. It has typically been used as a tool for hypothesis testing in genetics and social sciences. We propose here its first application to brain research. Structural modeling quantifies the impact of links between variables in a causally ordered system[1]. Directional influences between variables are supposed and path coefficients representing the magnitude of these influences are derived from the covariances/correlations between the variables. By analogy in the brain, the system would represent any functional neural system with directional paths between areas determined from the anatomy. The influence of these pathways (path coefficients) under specific conditions would then be computed based on the covariances/correlations between areas of the system.

Autoradiographic mapping with 2-deoxyglucose (2-DG)[14] has proven useful in assessing relative activity changes in functional neural pathways under numerous experimental conditions. Recent examples of such applications of 2-DG mapping techniques include: activation of sensory and motor systems[17,19]; responses to damage and drugs[5,11]; and changes related to learning[8]. One advantage that 2-DG uptake mapping holds over most classical neuroscience techniques, such as electrophysiology, is that it allows for an examination of activity through the entire brain of a single animal.

In spite of this, few studies have taken full advantage of 2-DG data by analyzing functional interactions within the same brain[12]. Measures are obtained from many, if not all, functional systems within the brain. Yet analyses are traditionally restricted to comparisons of the activity of single structures between groups. In some respects, this amounts to treating each brain region as if it were an entity apart from the system. Therefore, important sources of information are neglected. What is needed is a within-subjects analytic approach, such as structural modeling, that examines the changes of entire systems in animals under different experimental conditions.

Structural modeling does not typically reveal temporal flow of information in a system. Rather, it reveals patterns of interrelations between structures within a system based on the restrictions of the model. Therefore, 2-DG data on the activity of structures within the auditory system can be examined with structural models. This approach can serve to determine the relation

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between the structures of the auditory system under different stimulus conditions.

For this paper, models for the auditory system were constructed and path coefficients obtained to determine how interactions between structures changed in relation to habituation of the acoustic startle reflex. Habituation consisted of the decrease in the startle reflex with repeated presentations of an acoustic stimulus. This process is regarded as one of the simplest and most universal forms of learning[6,7].

MATERIALS AND METHODS

Data were obtained from 3 groups of rats used in a previous 2-DG experiment[6]. Briefly, the experiment examined changes in cerebral 2-DG uptake due to long- and short-term habituation of the acoustic startle response. A full-body startle reflex was elicited in rats by a loud noise (100 dB, 1 s burst of white noise). The acoustic startle reflex showed both short-term (one session) and long-term (10 sessions) decrements to repeated noise presentations. Each session lasted 45 min and consisted of 270 noise bursts. The long-term group received 9 prior sessions with the acoustic stimulus before testing and the short-term group was tested at first presentation. The control group for the experiment was tested in the sound-attenuated chamber without acoustic stimuli.

The 2-DG data used were obtained from autoradiographs analyzed with the Quantimet 920 imaging system. This system provided optical density, calculated isotope content, ratios between the labeling of each structure and a reference white matter, and relative optical density index between the structure and the entire section. It should be emphasized that the units of 2-DG measurement used for calculating within-subject correlations are irrelevant for the models. Correlations between optical density or isotope incorporation or any further transformation of 2-DG data are mathematically equivalent within the same subject. This is a major advantage of structural modeling as there is no need to calculate so-called 'absolute' glucose utilization to establish correlations among structures. The correlations will be the same regardless of transformation of the data from the same subject. This within-subject approach is therefore relevant to a wide range of applications as activity units are irrelevant for assessing functional interrelations between structures in the same brain.

The present models used the optical density data reported by Gonzalez-Lima et al.[6]. Values were obtained from the dorsal and ventral cochlear nuclei (DCN and VCN), the lateral and medial superior olivary nuclei (LSO and MSO), the nucleus of the lateral lemniscus (LL), the external and central nuclei of the inferior colliculus (ICE and ICC), the medial geniculate nucleus (MG), and primary auditory cortex (AC). The directional paths (arrows) in the models were based exclusively on well-established anatomical paths between these areas[3,9,21,22] (see Figs. 1–3).

Structural models can be assessed for their goodness-of-fit with respect to the data on which the models are based. Once paths between the elements of the system have been theorized, coefficients for these paths are computed. A covariance/correlation matrix is then computed based on the solution for the model and compared with the observed (original) matrix. The closer the two matrices agree, the better the model fits the data[16]. Two indices of fit were used for the present study, the goodness-of-fit index (GFI) and the root-mean-square residual (RMR). The GFI represents the degree of difference between the observed and computed data matrix and can have a value ranging from zero to one (where one indicates a perfect fit[13]). RMR is the average difference between the computed and observed matrix. In this case a large RMR indicates a poor fitting model. It can only be interpreted in relation to the type of matrix used as data[13]. For a covariance matrix, the range of possible values will depend on the size of the observed variances and covariances. For a correlation matrix, the values would range between zero and two.

The conventional use of the GFI and RMR is to indicate whether or not the linkages of an hypothesized model are tenable. In this application of structural modeling, the directional pathways are already known based on the anatomy. The interest here is what the magnitude of influence for each path is within each brain and how this relationship changes between experimental conditions. As such, the GFI and RMR were used as relative indices of how much of the observed covariances could be accounted for by the major anatomical pathways of the auditory system.

All analyses were conducted using LISREL version 6.6[13]. Structural modeling allows for influences not accounted for directly to be incorporated into the model. This would include the combined influence of areas not measured but thought to have an impact on regions in the system (e.g. monoaminergic systems, reticular formation). Such influences are usually referred to as residuals, errors, or in the case of LISREL – psi[15,16]. With structural modeling these can either be estimated or fixed at some predetermined value. Values for psi with an average of 0.4 were obtained from simpler models of the auditory system using DCN, VCN, ICC, ICE, MG and AC. Psi's were therefore fixed at 0.4 for the more complex models. It is likely that this value would have changed (if psi were free) in the complex models since more variables were added, but with the large number of unknowns for each structural equation the

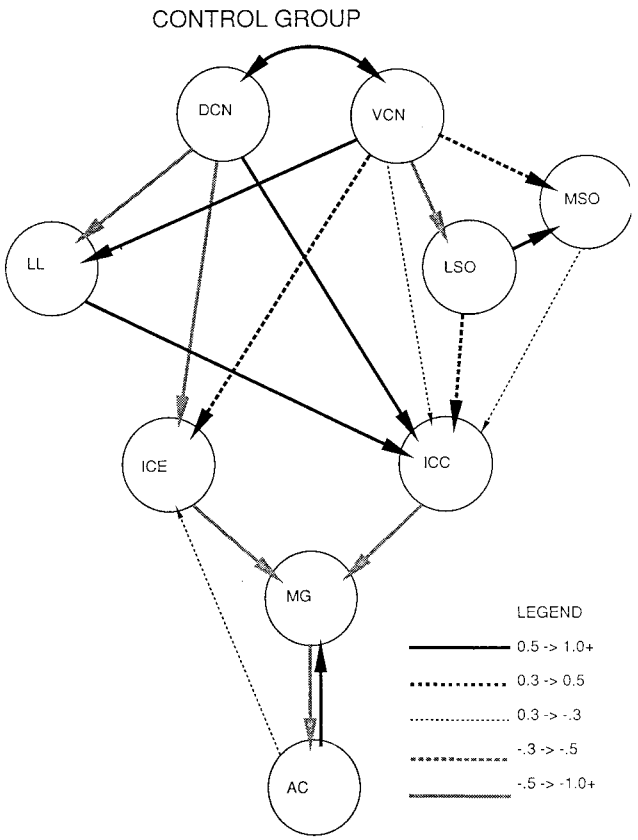

Fig. 1. Graphic representation of path model for the control group. Magnitude of the effect is indicated by the shading of each path. Values for the shading gradient are given in the legend in the bottom right of the figure. DCN, dorsal cochlear nucleus; VCN, ventral cochlear nucleus; LSO, lateral superior olive; MSO, medial superior olive; LL, nucleus of the lateral lemniscus; ICC, central nucleus of the inferior colliculus; ICE, external nucleus of the inferior colliculus; MG, medial geniculate; AC, primary auditory cortex.

values for psi could not be reliably estimated[2]. However, when the present models were computed fixing psi at lower values, the overall GFI's and the estimated path coefficients for each model were not drastically changed. When psi's were fixed at zero, unique solutions could not be obtained. This suggested that the value of 0.4 for psi was a reasonable estimate.

The relationship between DCN and VCN was depicted with a bi-directional path representing the influence of the cochlea. In all instances, the value for this path was equal to the correlation between DCN and VCN.

Three values for each auditory structure from each subject were obtained. Prior to calculating the correlation matrix (Table I) used as data for the structural models, the within-subjects variation due to multiple observations were partialled out[18]. This was accomplished by regressing each of the brain areas on two vectors representing the 3 observations for each subject and using the residuals from this to compute the partial correlations. This procedure allowed for number of observations for each group to triple while removing confounds due to this source of variance.

Estimates of path coefficients were produced using unweighted least-squares. A path coefficient represents the direct effect of a given variable on another variable to which it is immediately linked. Direct effects can be related to standardized regression coefficients in a multiple linear regression, in that they are the influence of one variable on another when all other variables are held constant[10]. For example, the direct effect of MG on AC represents the amount of change in AC directly attributable to MG when all other influences on both MG and AC are taken into account. For the present models, path coefficients which did not exceed 0.3 (absolute value) were not considered substantive.

In addition to direct effects, total effects of variables can also be calculated. Total effects represent the impact of a variable both through direct links and any influences transmitted through indirect routes (indirect effects). Technically, total effects are the algebraic sum of direct and indirect effects[1]. The total effect of VCN on ICC, then, is the sum of its direct impact on ICC and its indirect influences going through the superior olivary nuclei. This is extremely informative in that it can give an indication of the total influence of a brain area or pathway and whether the influence is modified at any stage in the system. Evaluations of total, direct and indirect effects are referred to as effects decomposition[4].

RESULTS

The partial correlation matrices for each group are shown in Table I. The results from the structural models are presented graphically in Figs. 1–3. Of the 3 models, the short-term group had the highest GFI and lowest RMR (0.990 and 0.092, respectively) followed by the long-term group's model (GFI = 0.967; RMR = 0.126). The model for the control group appeared to have the 'poorest' relative fit (GFI = 0.793; RMR = 0.228). These indices suggest that for the short- and long-term group's

TABLE I

Partial correlation matrices of 2-DG activity data from auditory structures for each group of rats

	MG	*AC*	*ICC*	*ICE*	*LL*	*LSO*	*MSO*	*DCN*	*VCN*
Control group (n = 9)									
MG	1.00								
AC	0.09	1.00							
ICC	−0.198	0.448	1.00						
ICE	−0.686	0.410	0.184	1.00					
LL	−0.561	−0.384	0.427	0.818	1.00				
LSO	−0.582	−0.384	0.239	0.177	−0.032	1.00			
MSO	0.031	0.362	0.434	0.388	0.339	0.351	1.00		
DCN	0.010	−0.067	0.436	−0.136	0.161	−0.251	−0.369	1.00	
VCN	0.189	0.393	0.613	−0.064	0.439	−0.531	−0.055	0.687	1.00
Short-term group (n = 15)									
MG	1.00								
AC	0.783	1.00							
ICC	0.749	0.889	1.00						
ICE	0.728	0.914	0.868	1.00					
LL	0.618	0.716	0.821	0.673	1.00				
LSO	0.506	0.741	0.806	0.833	0.771	1.00			
MSO	0.476	0.657	0.717	0.795	0.786	0.839	1.00		
DCN	0.711	0.681	0.868	0.757	0.825	0.744	0.735	1.00	
VCN	0.569	0.801	0.925	0.806	0.818	0.815	0.742	0.884	1.00
Long-term group (n = 15)									
MG	1.00								
AC	0.787	1.00							
ICC	0.572	0.306	1.00						
ICE	0.681	0.749	0.414	1.00					
LL	0.495	0.250	0.744	0.387	1.00				
LSO	0.711	0.623	0.716	0.699	0.647	1.00			
MSO	0.743	0.557	0.786	0.723	0.679	0.938	1.00		
DCN	0.392	0.244	0.696	0.427	0.860	0.700	0.712	1.00	
VCN	0.229	0.104	0.743	0.336	0.775	0.646	0.696	0.906	1.00

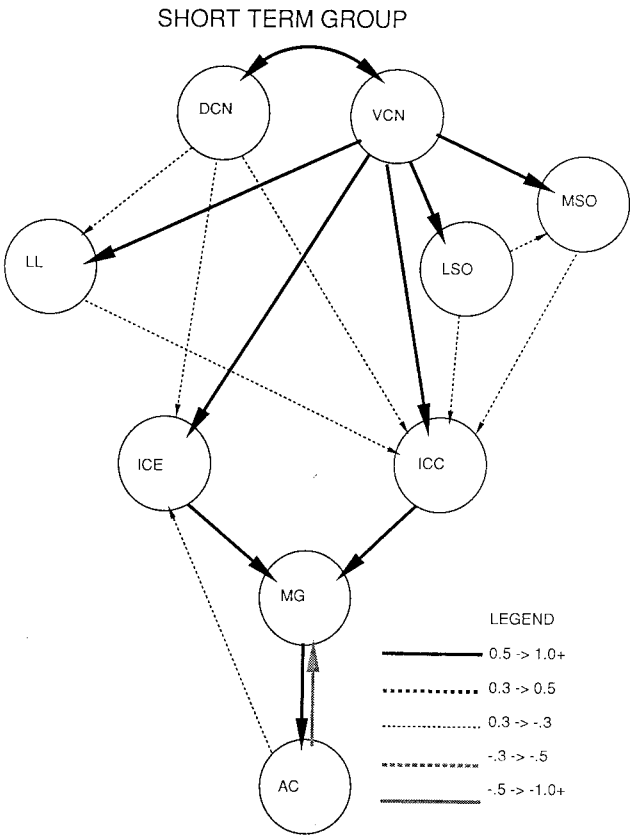

Fig. 2. Graphic representation of path model for the short-term group. Magnitude of the effect is indicated by the shading of each path. Values for the shading gradient are given in the legend in the bottom right of the figure.

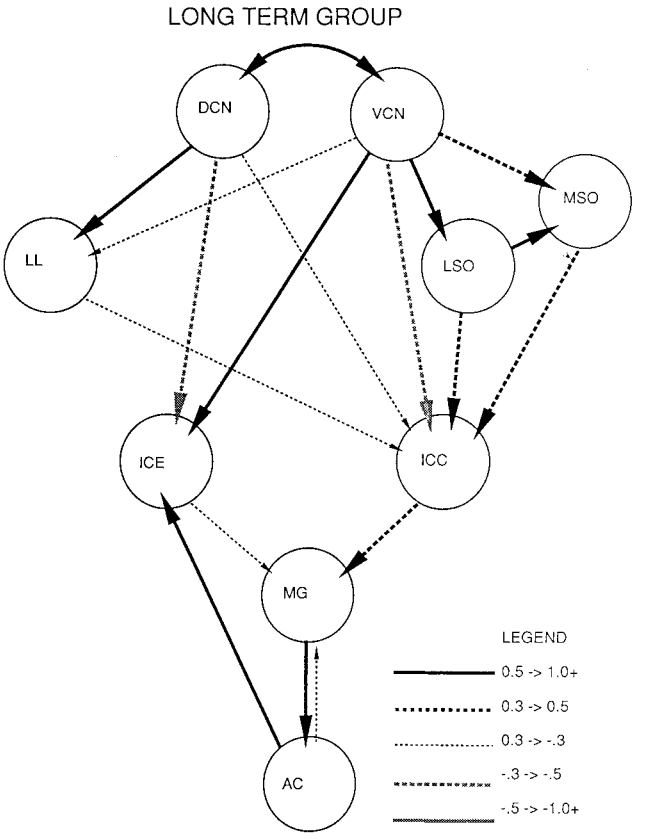

Fig. 3. Graphic representation of path model for the long-term group. Magnitude of the effect is indicated by the shading of each path. Values for the shading gradient are given in the legend in the bottom right of the figure.

models, most of the observed covariances could be accounted for by the anatomical paths between the auditory structures. In the control group it may be that other areas or anatomical paths not included in the model were acting upon the auditory system to a greater extent than for the other two groups.

The model for the control group (Fig. 1) can be thought to represent the baseline activity of the auditory system in the absence of the acoustic stimulus producing startle. The influence of the 'lemniscal system' (from VCN to ICC[22]) was apparently minimal and the extra-lemniscal paths dominated. Furthermore, the control group's model was characterized by a balance of positive and negative influences. DCN and VCN had both positive and negative direct effects. Most influences on AC were represented by negative relationships, while relationships among brainstem and midbrain regions were mostly positive.

In contrast to this, the lemniscal system was dominant in the model for the short-term group (Fig. 2) based on data from inexperienced animals exposed to the sound stimulus for the first time. All paths from VCN were positive, and the influence appeared to continue through ICC and ICE, and to AC via MG. The only negative influence was the descending path from AC to MG, a reversal of the case in the control group.

Fig. 3 shows the model for the long-term group based on data from experienced animals that had previous daily exposures to the sound stimulus. While the lemniscal system appeared to be active, the direct effect from VCN to ICC was negative. The positive influence appeared to be transmitted through the superior olivary nuclei (components of the extralemniscal system). Characteristics of the control group's model also appeared in the solution for the long-term habituated group. Both DCN and VCN had negative and positive direct effects. The unique component of this model was a strong positive descending influence of AC on ICE.

Tables II–IV give the coefficients for direct and total effects (direct plus indirect routes) for all groups. Examination of these tables substantiated the impressions gained from inspection of Figs. 1–3. Both the total and direct effects for the control group (Table II) showed negative and positive influences especially in regards to total effects. There also appeared to be numerous interactions between brainstem and midbrain areas indi-

TABLE II

Effects decompostion of interrelations of auditory structures in the control group

Values given are coefficients for total and direct effects. Rows list structures being affected and columns list origin of effects. Effects that cannot occur given the direct and indirect anatomical connections used for the present model are indicated by a dash (–).

	DCN	*VCN*	*LL*	*LSO*	*MSO*	*ICE*	*ICC*	*MG*	*AC*
Total effects									
LL	–0.859	1.108	–	–	–	–	–	–	–
LSO	–	–0.441	–	–	–	–	–	–	–
MSO	–	–0.029	–	0.907	–	–	–	–	–
ICE	–0.835	0.673	0.072	0.106	0.025	0.217	0.139	–0.173	0.236
ICC	0.121	0.373	0.515	0.763	0.178	–	–	–	–
MG	0.388	–0.467	–0.205	–0.305	–0.071	–0.623	–0.399	–0.503	0.685
AC	–0.285	0.343	0.151	0.224	0.052	0.457	0.293	–0.365	–0.503
Direct effects									
LL	–0.859	1.108	–	–	–	–	–	–	–
LSO	–	–0.441	–	–	–	–	–	–	–
MSO	–	0.371	–	0.907	–	–	–	–	–
ICE	–0.700	0.510	–	–	–	–	–	–	0.220
ICC	0.562	0.074	0.515	0.601	0.178	–	–	–	–
MG	–	–	–	–	–	–1.25	–0.803	–	1.971
AC	–	–	–	–	–	–	–	–0.735	–

cated by the large total effects relative to the short-term group.

For the short-term group (Table III), the dominance of the effect originating at VCN was obvious. Total effects of VCN were relatively equal for all possible routes (direct and indirect). In contrast neither DCN, nor any other brainstem region, seemed to have a substantial impact on upstream areas. Most of the total effects for these areas were close to zero or failed to exceed the cutoff point. Of interest as well was the apparent reduction of the total effect of regions in the midbrain and forebrain. Direct effects of MG on AC, AC on MG, and ICC and ICE on both areas were larger than the corresponding total effect. Since these areas are part of a loop-system it is likely that the loop acted to attenuated signals passed between these structures (for discussion of loop-effects see refs. 2, 10). Attenuation existed in all 3 groups, but was most pronounced in the short-term

TABLE III

Effects decompostion of interrelations of auditory structures in the short-term group

Values given are coefficients for total and direct effects. Rows list structures being affected and columns list origin of effects. Effects that cannot occur given the direct and indirect anatomical connections used for the present model are indicated by a dash (–).

	DCN	*VCN*	*LL*	*LSO*	*MSO*	*ICE*	*ICC*	*MG*	*AC*
Total effects									
LL	0.215	0.645	–	–	–	–	–	–	–
LSO	–	0.840	–	–	–	–	–	–	–
MSO	–	0.804	–	0.242	–	–	–	–	–
ICE	0.086	0.783	–0.006	–0.003	0.002	–0.126	–0.083	–0.098	–0.083
ICC	0.221	0.690	0.107	0.060	–0.310	–	–	–	–
MG	0.102	0.603	0.023	0.013	–0.007	0.481	0.218	–0.626	–0.530
AC	0.121	0.713	0.028	0.016	–0.008	0.569	0.257	0.442	–0.626
Direct effects									
LL	0.215	0.645	–	–	–	–	–	–	–
LSO	–	0.840	–	–	–	–	–	–	–
MSO	–	0.600	–	0.242	–	–	–	–	–
ICE	0.133	0.941	–	–	–	–	–	–	–0.222
ICC	0.198	0.588	0.107	0.068	–0.031	–	–	–	–
MG	–	–	–	–	–	1.286	0.582	–	–1.13
AC	–	–	–	–	–	–	–	1.182	–

TABLE IV

Effects decompostion of interrelations of auditory structures in the long-term group

Values given are coefficients for total and direct effects. Rows list structures being affected and columns list origin of effects. Effects that cannot occur given the direct and indirect anatomical connections used for the present model are indicated by a dash (–).

	DCN	*VCN*	*LL*	*LSO*	*MSO*	*ICE*	*ICC*	*MG*	*AC*
Total effects									
LL	0.545	0.299	–	–	–	–	–	–	–
LSO	–	0.794	–	–	–	–	–	–	–
MSO	–	0.788	–	0.551	–	–	–	–	–
ICE	–0.396	0.902	0.05	0.121	0.077	0.08	0.285	0.363	0.528
ICC	0.347	0.282	0.243	0.590	0.373	–	–	–	–
MG	0.105	0.348	0.144	0.349	0.221	0.232	0.592	0.047	0.069
AC	0.072	0.240	0.09	0.240	0.152	0.160	0.407	0.720	0.047
Direct effects									
LL	0.545	0.294	–	–	–	–	–	–	–
LSO	–	0.794	–	–	–	–	–	–	–
MSO	–	0.350	–	0.907	–	–	–	–	–
ICE	–0.433	0.782	–	–	–	–	–	–	0.504
ICC	–0.215	–0.389	0.243	0.590	0.373	–	–	–	–
MG	–	–	–	–	–	0.222	0.565	–	–0.046
AC	–	–	–	–	–	–	–	0.688	–

group. This is especially evident from the effects of ICE on MG. The total effect was 0.481, while the direct effect was 1.286. This leaves an indirect effect of –0.805 (total minus direct). The only route by which this could be transmitted is from AC. Therefore, there may have been a modification of the extra-lemniscal influence at the level of the ICE, or at the MG as well.

The modification of ascending effects for the long-term habituated group is readily observed by comparison of the total effects of VCN on other regions (Table IV). The total effect of VCN seemed to decrease in 'higher' brain areas (ICC, MG and AC). The total effect of VCN on LSO was 0.794 and was highest at ICE (0.902), but at ICC it reduced to 0.282, and at AC was down to 0.240. There were, however, large indirect effects of VCN. While the total effects of VCN are all positive, the direct effect from VCN to ICC is negative (–0.389). The total effect was 0.289. Thus there was a large indirect effect (0.671), through the superior olivary nuclei. VCN also had a total effect of 0.348 on MG, which also represented an indirect effect since these areas were not directly connected.

The involvement of the superior olivary nuclei, specifically LSO, was also evident upon examination of total and indirect effects. LSO had a total effect of 0.349 on MG. Since these two regions were not directly linked this represented an indirect effect transmitted through both MSO and ICC. This suggests that, in the long-term group, part of the signal from VCN was passed to and potentially modified by the LSO. It may be that another site of transformation involved the ICE since it received a large influence from VCN (0.782 direct), but did not appear to translate that to the MG. Cortical involvement is also likely as the long-term group was the only one to show a large descending influence from AC to ICE.

DISCUSSION

The application of structural modeling to 2-DG data revealed relationships that were not obvious through conventional data analysis. It appears that with long-term habituation, auditory processing is shifted from the lemniscal to the extra-lemniscal pathways with strong involvement from the superior olivary nuclei and the ICE. As well, it seems that the auditory system in a baseline state (control group) works to maintain an equilibrium state through both positive and negative influences, and perhaps contributions from extra-auditory systems.

The relationships revealed by the models can be added to the findings of Gonzalez-Lima et al.[6]. In that study, it was found that the largest difference between long- and short-term groups was in the LSO. It was speculated that this may be a reflection of the activation of the olivocochlear bundle in the long-term group. While this remains a possibility, it also appears that part of this effect may be related to the shift of information flow from the direct route (VCN to ICC) to the indirect route (VCN to LSO to ICC) as well as the direct effect from LSO alone. This activity change, therefore, may be a reflection of both the activation of the descending olivocochlear bundle, and processing and modification of the ascending signal.

Consistent with differences in the ICC and ICE found by Gonzalez-Lima et al.[6], different patterns of relationships between influences acting on ICC and ICE and the influences of these areas on MG and AC may suggest further modification of the auditory signal at this level. The effect from VCN to terminal sites appeared to be relatively unaffected in the short-term group. However, in the long-term group, this signal appeared to be modified substantially at various steps in the pathway. The descending influence of AC to ICE may have acted to attenuate the signal. This influence may act to reduce the 'arousal' component associated with the signal since the ICE has been associated with the extra-lemniscal system. This system is proposed to relay non-specific qualities of the auditory stimulus, and may be related to stimulus significance[22]. In the short-term group, the effect of ICE was larger than the long-term group. This may imply that the arousing component of the signal was transmitted to higher auditory centers in the short-term group, but not in the long-term habituated group.

Evaluation of structural modeling application

Structural modeling allows for the extrapolation of much more information from any experiment where data are obtained from complete pathways. Since structural modeling examines variables in the context of the system, it is possible to view interactions between structures from a quantifiable level. Principles that are an integral part of any neural system can also be evaluated; for example, the effects of feedback loops. In the auditory system model, it appeared that the feedback loops acted to attenuate to overall strength of the signal, as determined through effects decomposition.

Caution must be exercised when interpreting changes in 2-DG uptake, as well as positive and negative path coefficients, in terms of pre- or postsynaptic electrophysiological changes. At the cellular level, uptake of 2-DG in neural tissue primarily visualizes the activity of the sodium-potassium pump in the cell membrane[8,20]. Given the larger surface-to-volume fraction of cell membrane in the neuropil, dominant 2-DG uptake commonly is in perisynaptic neuropil rather than cell bodies[8,12]. While this appears to be the case in the auditory system, it has also been demonstrated that 2-DG uptake and the firing rate of auditory neurons are tightly coupled in response to sound[20]. This seems to be a result of the close input–output relation between pre- and postsynaptic activity of auditory neurons under normal sound stimulation[20]. However, such information is unnecessary to determine what the strength of a particular path coefficient is. Once placed in the context of the researcher's knowledge of the physiology of the system, the relative impact of the pathway and its influence under certain experimental conditions can be further evaluated.

It should be emphasized that positive and negative path coefficients in no way imply excitatory or inhibitory influences in the electrophysiological sense. Interpreting positive and negative path coefficients are best likened to the evaluation of positive and negative correlations. When two variables both increase in size in some proportional fashion, they are positively correlated. Conversely, when variables show the reverse relation, one variable increases while the other decreases, they are said to be negatively correlated. For path coefficients the relationship can be stated more specifically: a positive coefficient signifies that a unit increase in one variable leads to a 'direct' proportional increase in variables to which it is linked; for the negative coefficient, a unit increase in one variable leads to a 'direct' proportional decrease in variables to which it is linked. Positive and negative path coefficients, therefore, indicate the direction of the covariance relationship between the elements of the structural model.

As it currently stands, statistical evaluation of path solutions when unweighted least-squares estimation is used is not possible. Other estimation techniques such as generalized least-squares and maximum likelihood provide estimates of standard errors for coefficients and coefficients of determination (R^2). However, when sample sizes are small, these techniques may produced biased variance estimates thus rendering statistical evaluation difficult[2,15]. Methods of variance estimation for unweighted least-squares and other such techniques (e.g. two-stage least-squares) are currently under development.

When constructing a structural model, a conflict arises between the anatomical completeness of a model and its interpretability. An overly simple model may be easy to interpret, but its usefulness is limited. Conversely, a model which includes all anatomical connections will be uninterpretable. The present models represent a compromise between these two extremes. There are strategies which allow additional structures or paths to be added to an already established model[10]. Once a solution has been obtained for a simple model, values for that solution could be fixed and more structures or paths added. In such cases, this allows for the evaluation of the impact of the additions to the model given a particular state. Such a strategy could potentially be extended to include interactions between entire systems.

Finally, confirmation of the solutions obtained from this study are needed to ensure the stability of the present models and the validity of the application of structural models to brain research. It would be valuable to conduct the same analysis with different acoustic stimuli to see how these relationships hold. Moreover, some auditory structures known to have different connections (such as

subnuclei of the medial geniculate) could be further subdivided and non-auditory structures added to the current model to account for some of the extra-auditory influences[7].

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