A Hybrid Generative/Discriminative Method for Classification of Regions of Interest in Schizophrenia Brain MRI

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Abstract. Schizophrenia research based on magnetic resonance imaging (MRI) traditionally relies on the volumetric analysis of brain matter, either characterizing the whole intracranial volume or studying the attributes of small regions of interest (ROI), corresponding to well-known functional parts in the brain. In this work, we addressed the second scenario, proposing a novel approach able to automatically distinguish schizophrenic patients from normal controls using multiple ROIs. We explore a hybrid generative/discriminative approach, exploiting state of the art generative models via Fisher kernel and support vector machines (SVM). Experimental results, on a dataset of 124 subjects and 7 ROIs, are really encouraging, also in comparison with pure discriminative methods. Moreover, our results find some agreements with previous medical studies in schizophrenia research.

Key words: Hybrid generative/discriminative methods, Fisher kernel, support vector machine, schizophrenia research, brain MRI

1 Introduction

Computational neuroanatomy using magnetic resonance imaging (MRI) is a growing research field that employs image analysis methods to quantify morphological characteristics of different brains [1]. The ultimate goal is to identify structural brain abnormalities by comparing normal subjects with patients affected by a certain disease.

Roughly speaking there are two main categories of methods: (i) methods based on the analysis of regions of interest (ROI), and (ii) methods based on Voxel-based-Morphometry (VBM)[2]. ROI based methods focus on a limited set of brain subparts which are manually traced by experts. Methods based on VBM use the whole brain after a normalization procedure which maps the current brain onto a standard reference, namely the *stereotaxic* space. In this fashion, a voxel-by-voxel correspondence is available among the analyzed subjects.

In this work, we apply pattern recognition techniques to the problem of discriminating subjects affected by schizophrenia. We build our framework on top

of several previous investigations that confirmed the presence of abnormalities in these subjects [3,4,5,6,7,8,9] and extend it to classify healthy (i.e., controls) and unhealthy (i.e., patients) subjects.

Several works have been proposed recently for human brain classification in the context of schizophrenia research [10,11,12]. Beside standard volumetric methods [2,4], the most promising approaches focus on: (i) shape characterization [11], (ii) surface computation [12], and (iii) high dimension pattern classification [10]. In [11] a ROI-based morphometric analysis is introduced by defining a spherical harmonics and a 3D skeleton as shape descriptors. Improvement of such shape-descriptor-based approach with respect to classical volumetric techniques is experimentally shown. In [12] a support vector machine (SVM) has been proposed to classify cortical thickness which has been measured by calculating the Euclidean distance between linked vertices on the inner and outer cortical surfaces. In [10] a new morphological signature has been defined by combining deformation-based morphometry with SVM. In this fashion, multivariate relationships among various anatomical regions have been captured to characterize more effectively the group differences.

In this work, we go beyond volumetric measurements by classifying intensity histograms of the given ROIs. In order to be able to compare intensity values effectively, we perform a preliminary scale normalization based on landmark matching between intensity histograms [13]. The main goal of this study is to verify whether a significant improvement in brains classification can be obtained by exploiting more sophisticated pattern recognition techniques, instead of investigating more complex morphological features from MRI data. Inspired by recent trends in machine learning and pattern recognition research, we explore a hybrid generative/discriminative approach using the Fisher Score Space [14] to represent our data and employing support vector machines (SVM) [15,16] as classifiers. In particular, we based our framework on the so called *constellation* generative model which has been recently successfully applied for object recognition [17].

Generative and discriminative approaches are the two broad categories within which learning and classification methods fall: a generative approach will estimate the joint probability density function (pdf) of the data and class labels and will classify using the posterior probabilities obtained by Bayes' rule, while a discriminative approach will estimate a classification function directly. Generally, methods falling in the latter category obtain lower asymptotic errors. However, generative models remain popular for their ability to capture explicit data attributes and to incorporate missing features. Fisher kernels are designed to get the best of both worlds. In [14], it was shown that it is possible to extract Fisher scores from a generative model and convert them into a Fisher kernel, which may be used for classification by a kernel method, such as the SVM.

The rest of the paper is organized as follows. Section 2 describes our proposed hybrid approach, detailing both the generative and the discriminative parts. Section 3 describes the brains dataset, highlighting the standard medical protocol

which has been involved. Section 4 shows our experimental results, and finally conclusions are drawn in Section 5.

2 The proposed approach

In this paper, we propose to classify between healthy and diseased subjects by using an hybrid generative-discriminative framework. The most known and applied class of hybrid methods relies on the so called generative kernels [14], to be employed with a Support Vector Machine: the basic idea is to employ a generative model to define feature vectors and project objects to the resulting feature space. Therefore, a meaningful similarity/distance measure is defined, leading to a kernel. In the following all the parts of the proposed approach are detailed.

2.1 The generative part

For this part of the approach, the general idea is to choose a generative model capable of considering all the ROI at the same time, together with the relations between them. To this end, we based our framework on the same concepts behind the constellation probabilistic model [17], which foresees the encoding of one object in terms of a fixed number N of object subparts M_j, and relative spatial relationships. In general, object subparts are represented by their appearance A_i, while the spatial relations are encoded by the *shape* X_i (i.e., the relative subparts positions) of the overall configuration.

Here, we apply this intuition to MRI brain scans, by looking at the ROIs as subparts with a definite spatial configuration within the cerebral volume. Ideally, we expect the content and configuration of the ROIs in each subject to be informative enough to recognize patients from controls. It is worth to note that here X_i is not encoding morphological shape properties of subparts which instead are implicitly captured by the appearance A_i. In the following, we will call X_i as *relations* in order to avoid such ambiguity. Note that, while in [17] the correspondences between subparts in different objects is considered missing data, this is not our case, since ROIs identities (e.g., amygdala or thalamus) and matching between subjects are pre-determined. Consequently, instead of having to evaluate multiple combinatorial hypotheses, our model has to evaluate a single combination, incorporating this prior information by design.

Ultimately, we define the following expression for the log-likelihood of a particular class of L subjects $\{O_i\}_{i=1}^{L}$ (assumed to be independent and identically distributed):

$$\log p(\{O_i\}) = \log \prod_{i=1}^{L} p(O_i) = \sum_{i=1}^{L} \log p(O_i) = \sum_{i=1}^{L} \log \left[p(A_i \mid \theta_a) p(X_i \mid \theta_s) \right], \quad (1)$$

where $\theta = \{\theta_a, \theta_s\}$ is the set of appearance and relations model parameters, respectively. Training is performed by estimating the Maximum Likelihood solution θ^{MLE}.

Based on preliminary experiments, we observed that the relations information was not significant since they encode relative positions of ROIs which are the same for all the brains. Therefore we further simplified the model by using only the appearance model part. Note that, similar to [17], the appearances A_i are represented by PCA components obtained from the ROIs intensity histograms, in order to reduce data dimensionality and highlight consistent variations in the distribution of MRI values. As in [17], the appearance model $p(A_i \mid \theta_a)$ is then a Gaussian over the PCA components.

2.2 The discriminative part: the Fisher kernel

Fisher kernels [14] allow an effective general way of mixing generative and discriminative models for classification. In particular, the Fisher kernel approach measures the similarity between the objects by comparing them in the tangent space induced by the trained generative model, which is considered as a point in the Riemannian manifold defined by the chosen family of generative models. In practice, each object is represented by a feature vector, whose components are called Fisher scores, defined by the evaluation of the gradient of the model log-likelihood on the MLE solution. The dimensionality of this space equals the number of parameters. More in detail, given a probabilistic model, the Fisher scores $\phi(O_i)$ are defined through the following derivatives:

$$\phi(O_i) = \frac{\partial}{\partial \theta} \log p(O_i \mid \theta). \tag{2}$$

In particular, starting from Equation 1 and discarding the relations contribution, the Fisher score we obtain is

$$\phi(O_i) = \frac{\partial}{\partial \theta_a} \log p(A_i \mid \theta_a), \tag{3}$$

where θ_a represent the mean and variance parameters of the Gaussian appearance model. Following [14], we employ and train one generative model for both classes.

A kernel can be defined in various ways in the resulting space: the inner product was used in [14], while RBF and polynomial kernel have been proposed in [17].

3 Data and feature extraction

Quantitative data collection and processing in MRI based research implies facing several methodological issues to minimize biases and distortions. The standard approach to dealing with these issues is following well established guidelines, dictated by international organizations, such as the World Health Organization (WHO), or codified by respected institutions, such as leading universities. See [18] for further details.

	Group mean (and SD)*		Statistics		
Characteristic	Control ($n = 60$)	Schizophrenia ($n = 64$)	Test	*df*	*p*
Age, yr	39.95 (11.25) [range 23-60]	38.84 (11.96) [range 18-62]	$t = 0.53$	122	0.60
Male/female	32/28	43/21	$\chi^2 = 2.49$	1	0.11
Age at onset, yr		26.28 (9.17)			
Duration of illness, yr		13.37 (10.30)			

SD = standard deviation; *df* = degrees of freedom; *p* = value of significance.

* Unless otherwise indicated.

Table 1. Some demographic and clinical characteristics of the study groups. The Student's t-test of the age means rejects (at a two-tailed significance level of $p < 0.05$) the hypothesis that the study groups are significantly different in age, and Pearson χ^2 confirms the same for the gender differences.

The dataset used in this work is composed by MRI brain scans of 64 patients affected by schizophrenia and 60 healthy control subjects. Table 1 shows some demographic and clinical characteristics of the study groups. This database has been investigated several times, for example to produce large sample studies aimed at confirming previous reports of physiological abnormalities associated with the given mental illnesses [3,4,8]. Each of these studies focuses on a particular subpart of the brain, a so-called *region of interest* (ROI), whose abnormal activity is noted to affect cognitive processes. Images were acquired and transferred to PC workstations in order to be processed for ROI *tracing*. This latter procedure is the manual annotation of the images, performed by drawing contours enclosing the intended region. It is carried out by a trained expert following a specific protocol for each ROI. The raters generally achieved high interrater reliability, as defined by intra-class correlation coefficient of between 0.94 and 0.97 (see [18] for further details).

The ROIs traced in this dataset are 7 pairs (for the left and the right hemisphere respectively) of disconnected image portions describes as the following:

- Amygdala (*l_amyg* and *r_amyg* in short);
- Dorso-lateral PreFrontal Cortex (*l_dlpfc* and *r_dlpfc*);
- Entorhinal Cortex (*l_ec* and *r_ec*);
- Heschl's Gyrus (*l_hg* and *r_hg*);
- Hippocampus (*l_hippo* and *r_hippo*);
- Superior Temporal Gyrus (*l_stg* and *r_stg*);
- Thalamus (*l_thal* and *r_thal*).

In Fig. 1, we show a sample from the dataset, specifically the ROI volume of *r_stg* for subject 11. This volume is made up of 35 slices of size 41×40 and can be arranged as a montage of images (ordered from left to right, top to bottom). Within this bounding box, the ROI itself is irregularly shaped, as can be clearly seen from the corresponding binary masks on the right, artificially colored to highlight the ROI shape.

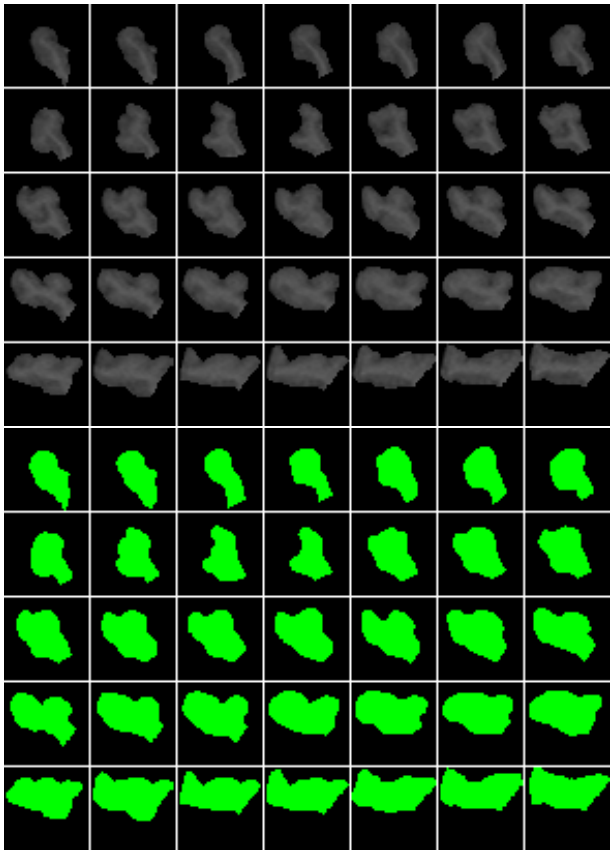

Fig. 1. Montage of the slices in the ROI volume ($41 \times 40 \times 35$) of *r_ stg* for subject 11. On the left, the MRI values; on the right, the corresponding binary masks.

Additionally, another important ROI that is traced is the *intracranial volume* (ICV), that is the volume occupied by the brain in the cranial cavity leaving out the brainstem and the cerebellum. This information is extremely useful for normalizing volume values against differing overall brain sizes.

3.1 MRI Intensity Scale Normalization

A major disadvantage of MRI compared to other imaging techniques is the fact that its intensities are not standardized. Even MR images taken for the same patient on the same scanner with the same protocol at different times may differ in content due to a variety of machine-dependent reasons, therefore, image intensities do not have a fixed meaning [13]. This implies a significant effect on the accuracy and precision of the following image processing, analysis, segmentation and registration methods relying on intensity similarity.

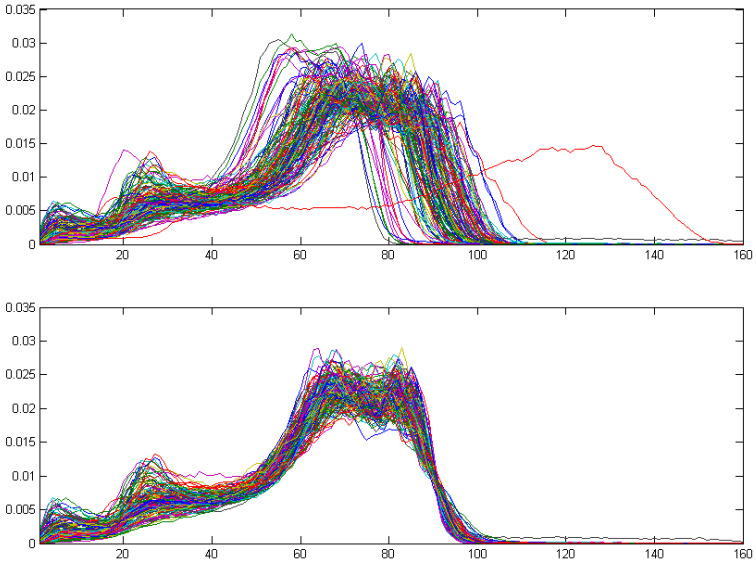

Fig. 2. ICV intensity histograms (treated like probability density functions), before and after the normalization process.

A successful technique used to calibrate MR signal characteristics at the time of acquisition employs *phantoms* [19], by placing physical objects with known attributes within the scanning frame. Unfortunately, this technique is not always exploited, which is our present case. Alternatively, it is possible to obtain good results by retrieving deformation mappings for the image intensities, that is, by developing histogram mappings [20,13].

In this work, we have decided to retrieve the rescaling parameters from the ICV histograms (see Fig. 2). In this way, we focus on the interesting content of the images, which usually contain "noise" in the form of bone and muscle tissue surrounding the brain matter proper. It is also easier to identify landmarks on the histograms that match the canonical subdivision of intracranial tissue into white matter, gray matter and cerebrospinal fluid. We have opted to select a simple rescaling mapping that conserves most of the signal in the gray matter - white matter area, corresponding to the two highest bumps in the range 60-90, since ROIs primarily contain those kinds of tissue.

4 Experimental results

In this part, we will show the effectiveness of the proposed approach using the above described dataset. The goal of the experimental evaluation is twofold: on one hand, we want to provide evidence that using all ROIs at the same time is advantageous with respect to using individual ROIs. On the other hand, we

want to show that an hybrid generative/discriminative model may outperform a simply discriminative approach. To this end, the proposed approach has been compared with two different techniques:

- Single ROI - SVM (RBFkernel): in this case the classification has been carried out using a single ROI. We used the same descriptor employed in the proposed approach, namely histograms whose dimensionality has been reduced with the PCA analysis.
- Multiple ROI - SVM (RBF kernel): in this case, the information coming from all the ROIs is merged. There are many methods for fusing information from different sources (see the huge Multi Classifier System Theory). In this case, we performed a feature level fusion, obtained by simply concatenating the vectors coming from different ROIs. This solution, even if simple, provided optimal results in several contexts (e.g. in Biometrics [21]). Subsequently, the concatenated PCA-reduced vectors have been classified using again a SVM (RBF kernel).

In all cases, the libSVM library [16] has been employed, with optimal parameters chosen via a cross validation analysis. Experiments were carried out in MATLAB and C, whereas accuracies figures for each test run where obtained through leave-one-out (LOO) cross-validation.

Results are proposed in Table 2. From the table, it is evident that most ROIs do not possess significant discriminative powers, but that using all of them at the same time achieves higher accuracy than the individual best ROI. Moreover it is evident that the hybrid generative discriminative approach outperforms the purely discriminative approach, confirming the findings obtained in other fields. Overall, results are suggestive, encouraging in a way, in fact they seem to support the main scientific claim that it is possible to identify schizophrenic patients from healthy people.

From the medical point of view, we can observe that the abnormalities in the amygdala, dorsolateral prefrontal cortex and hippocampus (the three individually most discriminative ROIs in our study) in particular in the left side, are among the most consistent findings in MRI studies on schizophrenia [22,23], suggesting that these structures play a major role for the pathophysiology of the disease [24]. In particular, the dorsolateral prefrontal cortex, along with the thalamus and the hippocampus, is a critic component of the brain circuitry underlying higher cognitive functions, such as attention, executive function and context processing [25]. The amygdala plays a critical role in the neural system that is involved in emotional and in fear-related responses [26]; and the hippocampus is involved in long term memory and in regulating stress response [27,28].

5 Conclusions

In this paper, we proposed a novel approach aimed at discriminating between schizophrenic patients and healthy people based on analyses of brain MR images.

Method	ROI	Accuracy
SVM Single ROIs	*l_amyg*	70.97%
	r_amyg	58.87%
	l_dlpfc	68.55%
	r_dlpfc	47.58%
	l_ec	59.68%
	r_ec	58.06%
	l_hg	58.06%
	r_hg	60.48%
	l_hippo	62.10%
	r_hippo	50.00%
	l_stg	59.68%
	r_stg	56.45%
	l_thal	61.29%
	r_thal	59.68%
SVM Multiple ROIs	*all*	77.42%
Hybrid Approach Multiple ROIs	*all*	80.65%

Table 2. Leave-one-out cross-validation accuracies. Our hybrid approach performs best. Taking all the ROIs performs better than considering them individually.

The proposed approach combines the contribution of different ROIs by exploiting a hybrid generative discriminative method, able to merge the descriptive power of a generative model with the classification accuracies of a discriminative approach. Experimental evaluations on a rather large dataset confirm the appropriateness of the proposed approach, also in comparison with other techniques. Moreover, we have shown that significative improvements can be obtained by focusing on effective classification strategies rather than on the search of complex MRI features. As future work, we envisage a more complex probabilistic modeling, eventually introducing clinical data (e.g., age, gender, illness duration, etc.), to explain variabilities in the data that influence the individual ROIs and hence their overall configuration.

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References

1. Giuliania, N.R., Calhon, V.D., Pearlson, V.D., Francisd, A., Buchanan, R.W.: Voxel-based morphometry versus region of interest: a comparison of two methods for analyzing gray matter differences in schizophrenia. Schizophr. Res. **74** (2005) 135–147

2. Ashburner, J., Friston, K.J.: Voxel-based morphometry - the methods. Neuroimage **11** (2000) 805–821
3. Agarwal, N., Rambaldelli, G., Perlini, C., Dusi, N., Kitis, O., Bellani, M., Cerini, R., Isola, M., Versace, A., Balestrieri, M., Gasparini, A., Mucelli, R., Tansella, M., Brambilla, P.: Microstructural thalamic changes in schizophrenia: a combined anatomic and diffusion weighted magnetic resonance imaging study. Journal of Psychiatry & Neuroscience **33**(5) (2008) 440–448
4. Baiano, M., Perlini, C., Rambaldelli, G., Cerini, R., Dusi, N., Bellani, M., Spezzapria, G., Versace, A., Balestrieri, M., Mucelli, R., Tansella, M., Brambilla, P.: Decreased entorhinal cortex volumes in schizophrenia. Schizophr. Res. **102** (2008) 171–180
5. Bernasconi, N., Bernasconi, A., Andermann, F., Dubeau, F., Feindel, W., Reutens, D.C.: Entorhinal cortex in temporal lobe epilepsy: a quantitative MRI study. Neurology **52**(9) (June 1999) 1870–1876
6. Brambilla, P., Harenski, K., Nicoletti, M., Sassi, R.B., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S., Soares, J.C.: MRI investigation of temporal lobe structures in bipolar patients. Journal of Psychiatric Research **37** (2003) 287–295
7. Emmorey, K., Allen, J.S., Bruss, J., Schenker, N., Damasio, H.: A morphometric analysis of auditory brain regions in congenitally deaf adults. Proceedings of the National Academy of Sciences of the United States of America **100** (2003) 10049–10054
8. Potkin, S.G., Turner, J.A., Brown, G.G., McCarthy, G., Greve, D.N., Glover, G.H., Manoach, D.S., Belger, A., Diaz, M., Wible, C.G., Ford, J.M., Mathalon, D.H., Gollub, R., Lauriello, J., O'Leary, D., Erp, T.G.V., Toga, A.W., Preda, A., Lim, K.O.: Working memory and DLPFC inefficiency in schizophrenia: The FBIRN study. Schizophr. Bulletin **35**(1) (2009) 19–31
9. Prasad, K.M., Sahni, S.D., Rohm, B.R., Keshavan, M.S.: Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. Psychiatry Research **140**(2) (2005) 147–155
10. Fan, Y., Shen, D., Gur, R.C., Gur, R.E., Davatzikos, C.: COMPARE: classification of morphological patterns using adaptive regional elements. IEEE Trans. on Medical Imaging **26**(1) (2007) 93–105
11. Gering, G., Styner, M., Lieberman, J.: Shape versus size: Improved understanding of the morphology of brain structures. In: Medical Image Comp. Computer-Assisted Intervention (MICCAI). (2001)
12. Yoon, U., Lee, J., Im, K., Shin, W., Cho, B.H., Kim, I.Y., Kwon, J.S., Kim, S.I.: Pattern classification using principal components of cortical thickness and its discriminative pattern in schizophrenia. Neuroimage **34** (2007) 1405–1415
13. Nyúl, L.G., Udupa, J.K., Zhang, X.: New variants of a method of mri scale standardization. IEEE Trans. Med. Imaging **19**(2) (2000) 143–150
14. Jaakkola, T., Haussler, D.: Exploiting generative models in discriminative classifiers. In: Advances in Neural Information Processing Systems 11, MIT Press (1998) 487–493
15. Vapnik, V.: The nature of Statistical Learning Theory. Springer (1995)
16. Chang, C.C., Lin, C.J.: LIBSVM: a library for support vector machines. (2001) Software available at `http://www.csie.ntu.edu.tw/~cjlin/libsvm`.
17. Holub, A.D., Welling, M., Perona, P.: Hybrid generative-discriminative visual categorization. Int. J. Comput. Vision **77**(1-3) (2008) 239–258
18. Cheng, D.S., Bicego, M., Castellani, U., Cerruti, S., Bellani, M., Rambaldelli, G., Aztori, M., Brambilla, P., Murino, V.: Schizophrenia classification using regions of

interest in brain MRI. Technical report, Dipartimento di Informatica, University of Verona, Italy (2009)
19. Edelstein, W.A., Bottomley, P.A., Pfeifer, L.M.: A signal-to-noise calibration procedure for NMR imaging systems. Medical Physics **11** (1984) 180–185
20. Jager, F., Hornegger, J.: Nonrigid registration of joint histograms for intensity standardization in magnetic resonance imaging. IEEE Transactions on Medical Imaging **28**(1) (January 2009) 137–150
21. Ross, A., Nandakumar, K., Jain, A.K., Zhang, D.: Handbook of multibiometrics. Springer (2006)
22. Meisenzahl, E.M., Koutsouleris, N., Bottlender, R., Scheuerecker, J., Jäger, M., Teipel, S.J., Holzinger, S., Frodl, T., Preuss, U., Schmitt, G., Burgermeister, B., Reiser, M., Born, C., Möller, H.J.: Structural brain alterations at different stages of schizophrenia: A voxel-based morphometric study. Schizophrenia Res. **104**(1-3) (Sep 2008) 44–60
23. Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W.: A review of mri findings in schizophrenia. Schizophr. Res. **49**(1-2) (Apr 2001) 1–52
24. Lopez-Garcia, P., Aizenstein, H.J., Snitz, B.E., Walter, R.P., Carter, C.S.: Automated roi-based brain parcellation analysis of frontal and temporal brainvolumes in schizophrenia. Psychiatry Res **147**(2-3) (Oct 2006) 153–161
25. Procyk, E., Goldman-Rakic, P.S.: Modulation of dorsolateral prefrontal delay activity during self-organized behavior. J Neurosci **26**(44) (Nov 2006) 11313–23
26. Swanson, L.W., Petrovich, G.D.: What is the amygdala? Trends in Neurosciences **21**(8) (1998) 323–331
27. Sala, M., Perez, J., Soloff, P., di Nemi, S.U., Caverzasi, E., Soares, J.C., Brambilla, P.: Stress and hippocampal abnormalities in psychiatric disorders. Eur. Neuropsychopharmacology **14**(5) (Oct 2004) 393–405
28. Tulving, E., Markowitsch, H.J.: Episodic and declarative memory: role of the hippocampus. Hippocampus **8**(3) (1998) 198–204