A NEW COMPUTATIONAL MEASURE FOR DETECTION OF EXTRAPYRAMIDAL SYMPTOMS

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Abstract. Extrapyramidal symptoms (EPS) associated with antipsychotic medication can provoke severe discomfort and disability. Some instruments have been proposed to assess EPS, but they are not widely used in clinical settings. This paper aims to provide a translational tool for the detection of EPS: lacunarity of patients' handwritings. Lacunarity is a measure, taken from fractals studies, that describes the spatial complexity of an image. 63 patients and 50 controls participated in the study. Patients were divided into: patients under typical antipsychotics, under atypical antipsychotics, and without antipsychotics. Participants were asked to write down a story. The texts were binarized and lacunarity was calculated. Results showed higher heterogeneity in handwritings from all patients groups, relative to the control group. Moreover, handwritings from the patients who were on typicals showed a significantly higher lacunarity than handwritings from patients on atypicals. The lacunarity of written texts appears to be a promising measure for the detection and quantification of EPS.

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1   Introduction

Antipsychotics (AP) have been shown to be effective in the treatment of symptoms in several mental disorders, as schizophrenia or bipolar disorder [1,2,3]. However, they cause important side effects that limit compliance with the treatment. Extrapyramidal symptoms (EPS) are among the most prevalent side effects of AP medications [4,5,6]. Depending on their persistence and severity, EPS can result in discomfort, functional impairment and stigma, and consequently in non-compliance or switching of medication [7,8,9].

The side effect profile (especially EPS) serves to differentiate the conventional or typical AP from atypical ones, rather than their efficacy in treating symptoms. The first-generation or typical AP act by blocking dopamine receptors (especially D2, D3 and D4). The blockade of dopamine receptors in basal ganglia is associated with EPS. The second-generation or atypical AP have lower binding to dopamine receptors, when compared to typical AP, but higher affinity for serotonin 5-HT, alpha noradrenergic, muscarinergic M and histaminergic H1 receptors. Many randomized controlled trials have concluded that these second-generation agents provoke EPS side effects less frequently than typical ones [10].

The study of factors contributing to the pharmacological non-adherence is important because they constitute a major obstacle in treatment [11,12,13]. In the present paper we are mainly interested in the characterization of EPS because their aforementioned important role in non-compliance or switching of medication. With this aim, we propose the analysis of handwritten texts as a tool to discriminate the differential effect of AP on patient's movements.

The acute EPS represent a wide range of abnormal motor syndromes. When these symptoms appear within the first 4 days of treatment they should be considered as antipsychotic-induced until proven otherwise. The symptoms can include dystonia, Parkinsonism, and akathisia [14]. Late-onset EPS include tardive dyskinesia, a persistent syndrome of involuntary choreoathetoid movements of the head, limbs and trunk.

As we mentioned before, AP vary in their propensity to produce EPS. There is no correlation between AP efficacy and the production of EPS. Clinical assess of EPS usually relies upon observer-based ratings. Some of these ratings are the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia, the Simpson-Angus EPS scale (SAEPS) or the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS). However, the reliability and validity of these instruments has not been well established. In a recent study, some authors [15] tested three screening instruments for EPS in patients with schizophrenia, Parkinson's Disease and healthy controls; and they found that, apart from a single item of the LUNSERS, none of the screening tools had an adequate predictive value.

Another approach has been the kinematic analysis of handwriting, which requires patients to write on a digitizing tablet. It has been found [16] that the handwriting of schizophrenic patients is significantly less consistent (in the duration and length of strokes) and less efficient (in the trajectory of strokes) than that from controls. A more recent study [17] has proved that schizophrenic patients treated with risperidone showed more dysfluent handwriting movements than untreated schizophrenics and

healthy controls. Dysfluency was correlated with medication dose. However, more interestingly, the authors found no correlation between the observer-based severity ratings and medication dose, suggesting that these subjective ratings are inefficient tools to capture the increase of EPS with AP dose. The same authors [18] have also compared the effect of different atypical AP on handwriting. They found that handwriting movements were more impaired in patients treated with aripiprazole than in patients with olanzapine and quetiapine; and this impairment was dose-dependent.

Although it is well documented that atypical AP produce fewer EPS than typical ones, only one study (to our knowledge) has compared them on kinematical measures of handwriting. The previously mentioned study [16] found that patients on atypical AP only differed from patients with typical ones in the consistency of movements' duration.

In the present work, we propose the use of a different measure, lacunarity, based on the analysis of handwriting with a standard pen on a simple sheet of paper. Lacunarity is a measure originally introduced by Mandelbrot [19], and subsequently described by others [20,21,22], to describe the distribution of the gap sizes of fractals of the same dimension with different texture appearances. While lacunarity was originally developed to describe a property of fractals, it can be extended to the description of general spatial patterns, including, but not restricted, to those with fractal properties [23]. At a given scale, lacunarity represents the similarity of the parts from different regions of a geometric object. Therefore, lacunarity is a scale-dependent measure of spatial complexity or texture. Whereas a large value of lacunarity implies large gaps and clumping of points, a small value of lacunarity suggests a rather uniform distribution with shorter gaps. In a broader sense, it is a measure of the degree of non-homogeneity within an object. Allain and Cloitre [22] presented an algorithm to calculate lacunarity by utilizing a moving window (See Appendix 1 for details of this algorithm). In this study we want to explore whether this new measure can capture differences in EPS associated with typical and atypical antipsychotics.

2   Method

2.1   Sample

The clinical sample consisted of 63 patients clinically diagnosed with schizophrenia, bipolar disorder or depression. 18 of these patients were medicated with typical AP or a combination of typicals and atypicals, 34 patients were medicated only with atypicals, and 11 patients were not taking AP at all (no AP). Diagnoses were made according to DSM-IV criteria after clinical examinations and based on review of all available case files. Exclusion criteria were history of substance abuse other than nicotine, neurological disorders or a history of severe head trauma. All participants provided written informed consent. The study was approved by the local ethics committee. The control group consisted of 50 age and educational level-matched

participants. None of them had any mental problem diagnosed at the time of study and none was under medication. See Table 1 for detailled demographic information.

2.2   Instruments and Procedure

Writing tasks were performed on A4 white paper, where a rectangle of 15 cm wide by 7.5 cm high was drawn on the center of the sheet. This frame was the region of interest for the analysis. Participants were given a sheet, where they were asked to write socio-demographic information. Later they were given the second sheet of paper, with the rectangular frame. Participants were asked to write about their summer holidays. Participants were informed that it was important to write just over the frame printed on the sheet. They were also told that the task had no time limit. The group of patients performed the task in the hospitals of Linares and Jaén whereas the control group performed the task in the labs of the University of Jaén.

2.3   Image Processing

The first step was to reclassify the greyscale images into binary ones where the darkest pixels were given a value of 1 (occupied cells), and the rest of them a value of 0 (gaps). Greyscale images were binarized using a histogram-derived method [24]. Image preprocessing was done with ImageJ[1] software [25].

Lacunarity was then calculated for each image using the Allain and Cloitre algorithm, with a range of square moving-window sizes varying from $r = 2$ pixels up to 45% of the region of interest. For each image and for each moving-window size, lacunarity was calculated with 12 different grid orientations and obtained values were averaged. Lacunarity calculation was obtained using FracLac plug-in for ImageJ [26].

3   Results

Lacunarity values were submitted to an ANOVA with Group (typical, atypical, no AP, control) as a between participant factor. Obtained results (see Figure 1) showed a significant effect of Group [$F(3, 112)= 47.96$; $p<0.01$; $\eta_p^2=.56$]. Post hoc comparisons were conducted using Bonferroni adjusted alpha levels of .0125 per test (.05/4). Results indicated that the lacunarity was significantly higher in the typical group (M=.32; SE=.02) when compared with the atypical group (M=.27; SE=.01), $t(50)=2.33$; $p=.024$, with the no AP group (M=.23; SE=.01), $t(27)=3.45$; $p=.002$, and with the control group (M=.15; SE=.03), $t(66)=12.33$; $p<.001$. Although there were no significant differences between lacunarity in the atypical group and in the no AP group $t(43)=1.57$; $p=.12$, heterogeneity of written texts was significantly higher in the atypical than in the control

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[1] ImageJ and its source code are freely available and in the public domain (http://rsbweb.nih.gov/ij/)

group t(82)=9.54; p<.001. Finally, lacunarity was significantly higher in the no AP group than in the control group, t(59)=6.03; p<.001.
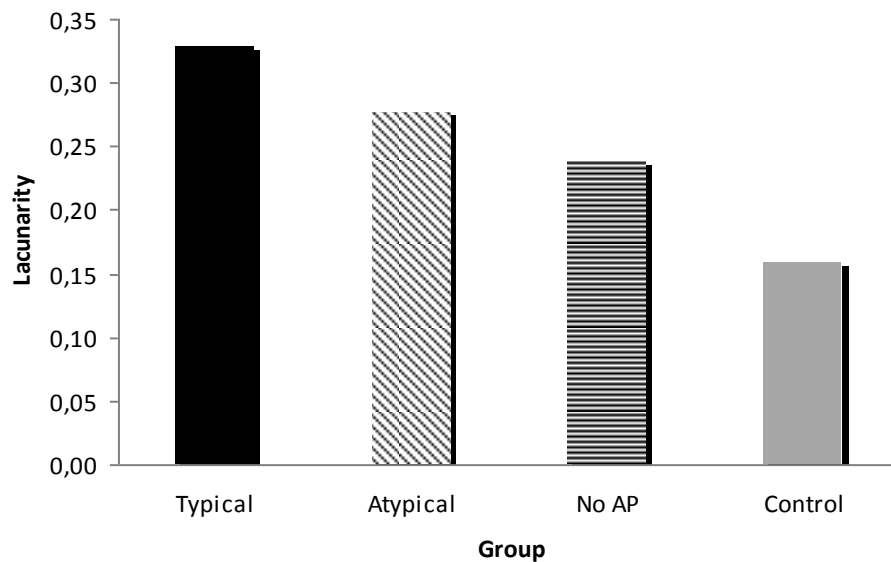
Fig. 1. Lacunarity mean in each condition

4   Discussion

In this study we have found differences in lacunarity of handwritten texts between the groups of the sample. First, lacunarity was higher in all patients groups, relative to the control group. Most interesting for our hypothesis, lacunarity was dependent on medication status. Handwritings from patients who were on typicals showed a significantly higher lacunarity than handwritings from patients on atypicals. On the other hand, lacunarity of handwritings from patients on atypicals did not differ from that of patients who were not taking AP at all. This would reflect that AP medication influences the homogeneity of handwriting; and these changes in handwriting patterns are captured by our new measure.

These results are in line with studies showing that atypical AP cause fewer EPS than typical ones. Although some research [16] [18] had previously evaluated handwriting

from patients with different antipsychotics, studies are really scarce and results have not been conclusive so far.

As we mentioned, rating scales have not proved to be sensitive enough to capture variability in EPS. Mechanical measurements are more sensitive and reliable, but they require complex devices (load cells, strain gauges, accelerometers, and electromyograms). The measure we propose would only need the scanning of handwriting texts, and the application of a series of formula. If proven sufficiently sensitive and reliable (in future studies), it would considerably improve EPS quantification in clinical practice.

Our study has some limitations. The sample is small, specially the groups of patients on typicals, or with no AP. This is due to difficulties to find these types of patients in a clinical setting nowadays; ethical issues prevent from changing the pharmacological treatment only with research purposes. Future studies could explore this topic with a larger sample; ideally lacunarity could also be examined in the same patients before and after initiated the pharmacological treatment.

Although more studies are needed to validate this new tool, we believe that these results are highly encouraging. According to our work, lacunarity is a useful measure to characterize EPS associated with different treatments. Their use could extend to the detection and quantification of EPS in other clinical disorders (Parkinson Disease, Alzheimer Disease, etc.). As the value of lacunarity is easy to obtain, and no special instrument or technical expertise is needed for data collection, we think that it could have a broad and quick implementation in clinical settings.

References

1. Tohen, M., Jacobs, T.G., Grundy, S.L., McElroy, S.L., Banov, M.C, Janicak, P.G., Sanger, T., Risser, R., Zhang, F., Toma, V., Francis, J., Tollefson, G.D., Breier, A.: Efficacy of olanzapine in acute bipolar mania: A double-blind, placebo-controlled study. Arch. Gen. Psychiatry. 57, 841-849 (2000)
2. Sachs, G.S., Grossman, F., Ghaemi, S.N., Okamoto, A., Bowden, C.L.: Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am. J. Psychiat. 159, 1146–1154 (2002)
3. Moritz, S., Andreou, C., Klingberg, S., Thoering, T., Peters, M.J.: Assessment of subjective cognitive and emotional effects of antipsychotic drugs. Effect by defect? Neuropharm. 72,179-86 (2013)
4. Jones, P.B., Barnes, T.R., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K.P., Murray, R.M., Markwick, A., Lewis, S.W.: Randomized controlled trial of effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch. Gen. Psych. 63, 1079–87 (2006)
5. Lewis, S.W., Barnes, T.R.E, Davies, L., Murray, R.M., Dunn, G., Hayhurst, K.P., Markwick, A., Lloyd, H., Jones, P.B.: Randomized controlled trial of effect of prescription of

clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr. Bull. 32, 715–23 (2006)

6. Lieberman, J.A., Tollefson, G., Tohen, M., Green, A.I., Gur, R.E., Kahn, R., McEvoy, J., Perkins, D., Sharma., T, Zipursky., R, Wei, H., Hamer, R.M., the HGDH Study Group.: Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized double-blind trial of olanzapine vs haloperidol. Am. J. Psychiat. 160, 1396–404 (2003)

7. Kapur, S. Remington, G.: Dopamine D-2 receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol. Psych. 50, 873-883 (2001)

8. Kapur, S., Mizrahi, R., Li, M.: From dopamine to salience to psychosis e linking biology, pharmacology and phenomenology of psychosis. Schizophr. Res. 79, 59-68 (2005)

9. Naber, D.: Subjective experiences of schizophrenic patients treated with antipsychotic medication. Int. Clin. Psychopharm. 13, 41–45 (1998)

10. Nasrallah, H.A., Brecher, M. Paulsson, B.: Placebo-level incidence of extra- Pyramidal symptoms (EPS) with quetiapine in controlled studies of patients with bipolar mania. Bipolar Dis. 8, 467–474 (2006)

11. Byerly, M., Suppes, T., Tran, Q.V., Baker, R.A.: Clinical implications of antipsychotic-induced hyperprolactinemia in patients with schizophrenia spectrum or bipolar spectrum disorders: recent developments and current perspectives. J. Clin. Psychopharm. 27, 639–661 (2007)

12. Kahn, R.S., Fleischhacker, W.W., Boter, H., Davidson, M., Vergouwe, Y., Keet, I.P., Gheorghe, M.D., Rybakowski, J.K., Galderisi, S., Libiger, J., Hummer, M., Dollfus, S., López-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rössler, A., Grobbee, D.E., EUFEST Study Group: Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 371, 1085–1097 (2008)

13. Lieberman, J., Stroup, S., McEvoy, J., Swartz, M., Rosenheck, R., Perkins, D., Keefe, R., Davis, S., Davis, C., Lebowitz, B., Severe, J., Hsiao, J.: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. New Engl. J. Med. 353, 1209 –1223 (2005)

14. Ghaemi, S.N., Hsu, D.I., Rosenquist, K.J., Pardo, T.B., Goodwin, F.K.: Extrapyramidal side effects with atypical antipsychotics in bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psych. 30, 209 – 213(2006)

15. Blanchet, P.J., Normandeau, L., Rompré, P.H.: Comparing three screening tools for drug-induced Parkinsonism in patients with advanced schizophrenia: A pilot study. Schizophr. Res. 137, 230-233 (2012)

16. Gallucci, R.M., Phillips, J.G., Bradshaw, J.L., Vaddadi, K.S., Pantelis, C.: Kinematic analysis of handwriting movements in schizophrenic patients. Biol. Psych. 41,830–833 (1997)

17. Caligiuri, M.P., Teulings, H., Dean, C.E., Niculescu, A.B. Lohra, J.: Handwriting movement analyses for monitoring drug-induced motor side effects in schizophrenia patients treated with risperidone. Hum. Movement Sci. 5, 633–642 (2009)

18. Caligiuri, M.P., Teulings, H.L., Dean, C.E., Niculescu, A.B., Lohr, J.B.: Handwriting movement kinematics for quantifying EPS in patients treated with atypical antipsychotics. Psych. Res. 177, 77-83 (2010)

19. Mandelbrot, B.B.: The fractal geometry of nature. Freeman, New York. (1983)

20. Gefen, Y., Meir Y., Mandelbrot, M. & Aharony, A.: Geometric implementation of hypercubic lattices with noninteger dimensionality by use of low lacunarity fractal lattices. Phys. Rev. Lett., 50, 145–148 (1983)

21. Lin, B. & Yang, J. : A suggested lacunarity expression for Sierpinski carpets. J. Phys. App., 19, L49–52 (1986)

22. Allain, C. and Cloitre, M.: Characterizing the lacunarity of random and deterministic fractal sets. Phys. Rev. 44, 3552-3558 (1991)

23. Plotnick, R.E., Gardner, R.H., Hargrove, W.W., Prestegaard, K. & Perlmutter, M.: Lacunarity analysis: A general technique for the analysis of spatial patterns. Phys. Rev. E, 53, 5461–5468 (1996)

24. Ridler, T. Calvard, S.: Picture treshholding using an interactive selection method. IEEE T. Sys Man Cy. 8, 630-632 (1978)

25. Abramoff, M.D., Magalhaes, P.J., Ram, S.J.: Image Processing with ImageJ. Biophotonics Intern. 11, 36-42 (2004)

26. Karperien, A. (1999-2014): FracLac for ImageJ.
http://rsb.info.nih.gov/ij/plugins/fraclac/FLHelp/Introduction.htm

APPENDIX 1

The algorithm is briefly summarized here with the aid of a 10 x 10 random binary map (see Figure 2). First, an r x r box is placed on the upper left corner. At this step the number of occupied sites in the 2 x 2 solid box is one. The box is then displaced along the object with some overlap, and the number of occupied sites is again counted (in this example, the number of occupied sites in the dashed box is two). This count is referred to as the box mass. This process is iterated for distinct values of r. If the size of the map is M, and it is squared-shaped, the total number of boxes of size r is N[r]:

$$N[r] = (M - r + 1)2 \qquad (1)$$

We can then produce a probability distribution of the box mass dividing the number of boxes of size r containing S occupied sites, n[S,r], by N[r]:

$$Q(S,r) = n[S,r] / N[r] \qquad (2)$$

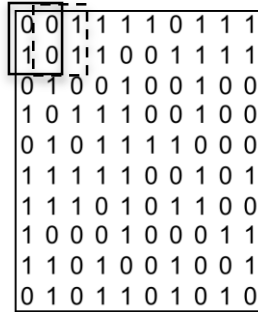We can then calculate the first moment Z(1) and the second moment Z(2) of this distribution.

$$Z(1) = \Sigma \, [S \times Q(S,r)] \qquad (3)$$

$$Z(2) = \Sigma \, [S2 \times Q(S,r)]$$

Lacunarity Λ depends on the box size r and is defined as:

$$\Lambda[r] = Z(2) / [Z(1)]2 \qquad (4)$$

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0 0 1 1 1 1 0 1 1 1
1 0 1 1 0 0 1 1 1 1
0 1 0 0 1 0 0 1 0 0
1 0 1 1 1 0 0 1 0 0
0 1 0 1 1 1 1 0 0 0
1 1 1 1 1 0 0 1 0 1
1 1 1 0 1 0 1 1 0 0
1 0 0 0 1 0 0 0 1 1
1 1 0 1 0 0 1 0 0 1
0 1 0 1 1 0 1 0 1 0
```

Fig. 2. Illustration of the gliding box method in a 10 x 10 random binary map. Solid box represents the first box with *r* = 2, and dashed box represents the same box moved one pixel to the right.

	Controls (n=50)	Typical AP[1] (n=18)	Atypical AP (n=34)	No AP (n=11)	Statistics
Gender	25 male	14 male	19 Male	4 male	$Chi^2(3)=5.82$; $p=.12$
Age (Years)	49.68^a; 3.15^b	48.39^a; 3.72	44.91^a; 2.44^b	48.45^a; 3.15^b	$F(3;112)<1$
Education level	27^c; 6^d; 17^e	12^c; 3^d; 3^e	16^c; 12^d; 6^e	3^c; 6^d; 2^e	$Chi^2(6)=.14.86$; $p=.2$
Handedness	42^f; 5^g; 3^h	15^f; 3^g; 0^h	29^f; 0^g; 4^h	9^f; 1^g; 1^h	$Chi^2(6)=.7,21$; $p=.30$
Age at onset (Years)	--	31.38^a; 4.14^b	27.82^a; 2.89^b	34.18^a; 3.08^b	$F(2;62)<1$
Duration of illness (Years)	--	16.72^a; 2.29^b	$16,56^a$; 1.66^b	14.82^a; 2.53^b	$F(2;62)<1$
Undifferentiated SZ[2]	--	8	13	2	
Paranoid SZ[2]	--	4	14	1	
Major Depression	--	4	1	1	
Bipolar Disorder	--	2	6	7	

Table 1. Demographics for sample participants. (1) AP: Antipsychotics. (2) SZ: Schizophrenia
(a) Mean; (b) Standard Error; (c) Elementary School; (d) High School; (e) University; (f) Right;
(g) Left; (h) Both.