



# Subclinical hypothyroidism and neurocognitive functioning in bipolar disorder



Diego J. Martino <sup>a, b, \*</sup>, Sergio A. Strejilevich <sup>a, c</sup>

<sup>a</sup> Bipolar Disorder Program, Institute of Neurosciences, Favaloro University, Buenos Aires, Argentina

<sup>b</sup> National Council of Scientific and Technical Research (CONICET), Argentina

<sup>c</sup> Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina

## ARTICLE INFO

### Article history:

Received 2 September 2014

Received in revised form

24 November 2014

Accepted 18 December 2014

### Keywords:

Thyroid  
Memory  
Attention  
Executive functions

## ABSTRACT

The aim of this study was to compare neurocognitive functioning between euthymic bipolar disorder (BD) patients with and without subclinical hypothyroidism (SCH). Patients with SCH had poorer performance than patients without SCH in measures of verbal memory, attention, language, and executive functions. These preliminary results suggest that SCH could have some impact on the neurocognitive performance of euthymic patients with BD and warrant further research in this field.

© 2014 Elsevier Ltd. All rights reserved.

Subclinical hypothyroidism (SCH) is defined as a state of increased serum thyroid-stimulating hormone (TSH) levels, with circulating thyroxine (T4) and tri-iodothyronine (T3) concentrations within the population reference range (Pearce et al., 2013). Historically, a relationship between overt hypothyroidism and neurocognitive impairments has been reported (Dugbartey, 1998), while evidence for an association between SCH and cognitive performance is less robust, with studies showing both positive and negative results (Baldini et al., 1997; Jorde et al., 2006). Although SCH is the most frequent thyroid dysfunction in bipolar disorder (BD), its role on the neurocognitive impairments of euthymic BD patients remains unexplored so far (Bonnin et al., 2010). Then, the aim of this post-hoc analysis was to compare the neurocognitive performance of euthymic BD patients with and without SCH.

The present sample comprised 53 patients with BD according to DSM-IV using the Structured Clinical Interview for DSM-IV. Patients were included if they were between 18 and 60 years of age, were euthymic (Hamilton Depression Rating Scale – HDRS – <8 and Young Mania Rating Scale – YMRS – <6) during at least 8 weeks, and had their serum TSH measured within 4 months before or after neurocognitive assessment. The sample was divided into two

groups: euthyroid BD (E-BD,  $n = 39$ ) and BD with previous diagnosis of SCH (SCH-BD,  $n = 14$ ), defined by serum TSH level  $>4$  mU/l with T4 and T3 within the population reference range. All patients included in the latter group were in treatment with L-thyroxine. Exclusion criteria were: antecedent history of substance abuse, neurological disease, or other unstable clinical condition that could affect cognitive performance. The study was approved by the Hospital Ethics Committee and all subjects gave written informed consent.

All subjects performed a neuropsychological battery selected to assess the following cognitive domains: 1) Attention: Forward Digit Span (Wechsler, 1955), and Trail Making Test part A (Reitan, 1958); 2) Verbal memory: Memory Battery of Signoret (Signoret and Whiteley, 1979); 3) Language: Boston Naming Test (Kaplan et al., 1983); and 4) Executive functions: Wisconsin Card Sorting Test (Heaton, 1981), Trail Making Test part B (Reitan, 1958), and Phonological Fluency (Benton et al., 1983). Additionally, estimated premorbid IQ was assessed with the WAIS vocabulary subtest (Wechsler, 1955).

There were no differences between patient groups in age (E-BD =  $39.92 \pm 11.43$ ; SCH-BD =  $37.64 \pm 12.26$ ;  $t = 0.63$ ;  $df = 51$ ;  $p = 0.53$ ), gender (E-BD = 58% female; SCH-BD = 77% female;  $X^2 = 1.57$ ;  $df = 1$ ;  $p = 0.21$ ), years of education (E-BD =  $14.90 \pm 2.23$ ; SCH-BD =  $14.86 \pm 2.14$ ;  $t = 0.58$ ;  $df = 51$ ;  $p = 0.95$ ), premorbid IQ (E-BD =  $56.03 \pm 6.29$ ; SCH-BD =  $54.93 \pm 6.81$ ;  $t = 0.55$ ;  $df = 51$ ;  $p = 0.59$ ), duration of illness (E-BD =  $10.97 \pm 6.74$ ; SCH-

\* Corresponding author. Gurruchaga 2463, 1°“C” (1425) Ciudad Autónoma de Buenos Aires, Argentina. Tel./fax: +54 11 4833 2424.

E-mail address: [diejmartino@gmail.com](mailto:diejmartino@gmail.com) (D.J. Martino).

**Table 1**

Neurocognitive evaluation of bipolar patients with (SCH-BD) and without (E-BD) subclinical hypothyroidism (values are expressed as mean, standard deviation is shown in brackets).

	E-BD (n = 39)	SCH-BD (n = 14)	MANOVA (df = 1)
<b>Verbal memory</b>			
Immediate Logical Memory	7.37 (1.96)	6.11 (1.76)	$F = 4.19$ ; $p = 0.046$
Delay Logical Memory	7.18 (2.12)	5.58 (1.43)	$F = 6.41$ ; $p = 0.015$
Serial Learning	10.33 (1.44)	9.62 (1.76)	$F = 2.17$ ; $p = 0.15$
Free Delay Recall	8.90 (1.80)	8.00 (2.20)	$F = 2.16$ ; $p = 0.15$
Recognition	11.87 (0.34)	11.62 (0.51)	$F = 4.31$ ; $p = 0.043$
<b>Attention</b>			
Forward Digit Span	6.23 (1.06)	5.46 (1.66)	$F = 3.79$ ; $p = 0.057$
Trail Making Part A	36.56 (11.34)	53.08 (32.41)	$F = 7.60$ ; $p = 0.008$
<b>Language</b>			
Boston Naming Test	52.62 (4.22)	49.54 (5.56)	$F = 4.40$ ; $p = 0.041$
<b>Executive functions</b>			
Phonological Fluency	17.10 (4.64)	12.77 (4.55)	$F = 8.59$ ; $p = 0.005$
Trail Making Part B	85.38 (26.88)	101.46 (55.62)	$F = 1.95$ ; $p = 0.17$
WCST-Perseverative Errors	9.69 (7.92)	10.38 (10.78)	$F = 0.062$ ; $p = 0.80$

BD =  $12.00 \pm 10.44$ ;  $t = -0.41$ ;  $df = 51$ ;  $p = 0.68$ ), previous manic/hypomanic (E-BD =  $3.00 \pm 2.14$ ; SCH-BD =  $3.71 \pm 2.99$ ;  $t = -0.98$ ;  $df = 51$ ;  $p = 0.35$ ) and depressive episodes (E-BD =  $4.09 \pm 2.06$ ; SCH-BD =  $4.14 \pm 2.57$ ;  $t = -0.82$ ;  $df = 51$ ;  $p = 0.93$ ), or subclinical symptoms assessed with the YMRS (E-BD =  $0.87 \pm 1.56$ ; SCH-BD =  $0.64 \pm 1.22$ ;  $t = 0.49$ ;  $df = 51$ ;  $p = 0.62$ ) and the HDRS (E-BD =  $1.92 \pm 1.96$ ; SCH-BD =  $1.71 \pm 1.86$ ;  $t = 0.35$ ;  $df = 51$ ;  $p = 0.73$ ). All patients were medicated with mood stabilizers; there were no between-group differences in terms of exposure to antidepressants (E-BD = 39%; SCH-BD = 50%;  $X^2 = 0.33$ ;  $df = 1$ ;  $p = 0.56$ ), antipsychotics (E-BD = 49%; SCH-BD = 64%;  $X^2 = 1.08$ ;  $df = 1$ ;  $p = 0.30$ ), and benzodiazepines (E-BD = 59%; SCH-BD = 43%;  $X^2 = 0.33$ ;  $df = 1$ ;  $p = 0.56$ ). Finally, both patient groups had similar levels of serum TSH (E-BD =  $2.42 \pm 1.28$ ; SCH-BD =  $2.71 \pm 1.59$ ;  $t = -0.67$ ;  $df = 51$ ;  $p = 0.50$ ). One-way multivariate analysis of variance was conducted, with all neurocognitive measures as dependent variables and patient group as a factor. A significant overall between-group difference in neurocognitive functioning was detected with multivariate analysis of variance (Pillai's  $F = 2.24$ ;  $df = 11, 41$ ;  $P = 0.031$ ). Group mean scores on each neurocognitive measure and the corresponding analysis of variance are shown in Table 1.

These preliminary results suggest that SCH could have some impact on the neurocognitive performance of euthymic patients with BD. In fact, patients with SCH had a profuse profile of cognitive impairments compared with euthyroid patients, though there were no significant differences in demographic and clinical variables of interest. It is interesting to note that these contrasting neurocognitive outcomes between patient groups were found in the absence of differences in serum TSH levels. This dissociation between serum TSH and neurocognitive performance could be due to methodological factors, since TSH measurements were made as a part of the routine treatment of patients and without the purpose of conducting the present analysis. Therefore, TSH levels were used as a proxy of thyroid function and not as a standardized measure. Alternatively, this dissociation could be explained by the fact that neurocognitive performance was more closely related to serum free T4 than to TSH levels, as suggested by some studies (Jensovsky et al., 2000). Finally, other studies found that replacement therapy had a

greater effect on the normalization of TSH levels than on the improvement of cognitive performance among patients with hypothyroidism (Jorde et al., 2006), which could also explain the dissociation observed in this analysis.

Some limitations of this post-hoc analysis should be taken into account, such as the small sample size, length of SCH, duration of treatment with L-thyroxine, and lack of measurements of some serum thyroid hormones (e.g. free T4). However, the results of this analysis warrant further research to assess the relationship between thyroid function and cognitive impairments, as well as the effect of replacement treatment with L-thyroxine on the neurocognitive functioning of BD patients with SCH.

### Role of the funding source

None.

### Contributors

DJM and SAS contributed to the design of the study and supervised the research project. DJM performed the data analysis and drafted the manuscript. Both authors contributed to and have approved the final manuscript.

### Conflict of interest

The authors report no financial or personal relationships, interests, and affiliations relevant to the subject matter of the manuscript.

### Acknowledgments

None.

### References

- Baldini IM, Vita A, Mauri MC, Amodei V, Carrisi M, Bravin S, et al. Psychopathological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry* 1997;21:925–35.
- Benton A, Hamsher K, Sivan A. Multilingual Aphasia Examination. 3rd ed. Iowa: AJA Associates; 1983.
- Bonnin CM, Martinez-Aran A, Sanchez-Moreno J, Torrent C, Franco C, Pacchiarotti I, et al. Bipolar disorder, cognitive functioning and hypothalamic-pituitary-thyroid axis. *Actas Esp Psiquiatr* 2010;38(4):223–8.
- Dugbartey AT. Neurocognitive aspects of hypothyroidism. *Arch Intern Med* 1998;158:1413–8.
- Heaton R. Wisconsin card sorting test. Odessa, FL: Psychological Assessment Resources; 1981.
- Jensovsky J, Spackova N, Hejdukova B, Ruzicka E. Effect of normalization of an isolated increase in TSH on the neuropsychological profile of patients. *Cas Lek Cesk* 2000;139:313–6.
- Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J Clin Endocrinol Metab* 2006;91:145–53.
- Kaplan E, Goodglass H, Weintraub S. The Boston Naming test. 2nd ed. Philadelphia: Leo & Febiger; 1983.
- Pearce SHS, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. ETA Guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2013;2: 215–28.
- Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Ski* 1958;8:271–6.
- Signoret J, Whiteley A. A memory battery scale. *Int Neuropsychol Soc Bull* 1979;2: 2–26.
- Wechsler D. Wechsler Adult Intelligence Scale-Revised. Cleveland: Psychological Corporation; 1955.