

## Hostility, Depression, Anger-In In Headache Subgroups With Bruxism And Craniomandibular Disorders.

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### Abstract

#### Introduction

**Aim:** Compare scores in hostility, depression and anger inward in tension-type headache, migraine, combination headache, occipital neuralgia, myofascial headache and controls without headache.

**Methods:** Clinical examination, questionnaires, evaluation of specific symptoms of headache, The Beck Depression Inventory, the Cook-Medley Instrument for hostility and a novel tool to assess anger held inward, were used to assess patients with tension-type headache (n=100), migraine (n=17), combination headache (n=41), occipital neuralgia (n=27), myofascial headache (n=42) and controls without headaches (N=54).

**Results:** We found a statistically and significant difference in hostility means ( $p < 0.0002$ ): Tension-type headache versus migraine ( $p < 0.05$ ), migraine versus controls ( $p < 0.001$ ), and occipital neuralgia versus controls ( $p < 0.05$ ). There was a statistically and significant difference regarding depression scores ( $p < 0.0001$ ). Depression scores were higher in migraine as compared with tension-type headache ( $p < 0.001$ ), in ON as compared with tension-type headache ( $p < 0.05$ ), in migraine as compared with myofascial headache ( $p < 0.05$ ), in Migraine as compared with the Control subgroup ( $p < 0.001$ ), in the Combination headache group as compared with the Control subgroup ( $p < 0.01$ ), in ON as compared with the Control subgroup ( $p < 0.001$ ) and when the myofascial headache group was compared with the Control subgroup ( $p < 0.05$ ). We found a statistically and significant difference when comparing means in anger- inward in the four headache subgroups and controls ( $p < 0.001$ ). Highest scores in anger-inward were observed in the migraine, combination headache and myofascial headache subgroups. Statistically significant differences were observed when the pairs of subgroups Combination versus tension-type headache ( $p < 0.05$ ); Myofascial versus Tension-type headache ( $p < 0.01$ ); Tension-type headache versus Control subgroup ( $p < 0.05$ ); Migraine versus ON headache ( $p < 0.001$ ); Migraine versus Control subgroup ( $p < 0.001$ ); combination versus ON headache ( $p < 0.001$ ); Combination headache versus Control subgroup ( $p < 0.001$ ); Myofascial versus ON headache ( $p < 0.001$ ); and Myofascial headache versus Control subgroup ( $p < 0.001$ ). All headache subgroups demonstrated higher scores in anger-in as compared with the Control subgroup.

**Conclusions:** Scores in hostility were the highest in the migraine and occipital neuralgia subgroups. All headache groups demonstrated higher scores in hostility as compared to the control one. The migraine and occipital neuralgia subgroups demonstrated the highest scores in depression, whereas the migraine, combination and myofascial headache subgroups demonstrated the highest scores in anger-taken inward. Psychological and psychiatric evaluation at least in some subgroups of Craniomandibular disorders and bruxing behavior individuals is warranted.

**Keywords:** Craniomandibular Disorders. Depression. Hostility. Anger-inward.

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### I. Introduction

Craniomandibular disorders (CMDs) are a heterogeneous set of diseases affecting the masticatory system and adjacent functionally anatomic structures which present a complex etiology as well as diagnosis and taxonomic problems<sup>1</sup>. Major CMD signs and symptoms include a complaint of pain, impairment of jaw movements, joint sounds and headache of musculoskeletal origin<sup>2</sup>. Bruxing behavior (BB) is an oral habit characterized by involuntary rhythmic/spasmodic nonfunctional gnashing, grinding, or clenching of the teeth. Chewing like movements in bruxers, may lead to occlusal trauma<sup>3</sup>. Most dangerous form of this disorder is

nighttime bruxism, which has a psycho-emotional and occlusal origin<sup>4</sup>. Bruxism is a movement disorder of the masticatory system related to an arousal response of the central nervous system possibly controlled by a multifactorial generator pattern in which some interacting factors contribute to its onset<sup>5</sup>. BB is characterized by teeth grinding and clenching during sleep as well as during wakefulness<sup>6</sup>. Hostility is a dispositional tendency characterized by behaviors such as aggression and attitudes such as cynicism and anger. Hostility, anger experience and anger expression seem to be involved in the maintenance of chronic pain<sup>7</sup>. Pain such as headache, can cause and/or maintain anger and hostility, but such reactions are associated with exacerbation of pain, disability and depression. Furthermore, under conditions of chronic stress, pain and hostility may predict chronic inflammation<sup>7</sup>. Patients with various chronic pain conditions are characterized by high levels of trait anger and hostility. The tendency to suppress anger or externalize angry feelings seems to be a determinant of chronic pain severity<sup>8</sup>. Depression, headache and other neuropsychological comorbidities are fundamentally neurophysiological disorders. Patients with depression are more vulnerable to general pain and traumatic pain sequelae particularly head and neck pain. Depression and headache, share many common clinical features, including mood disturbance and sleep dysfunction. Relief from headache in many patients with severe headache and depression can bring immediate relief of depression<sup>9</sup>. In several types of headaches and facial pain, some etiologic factors may be present and complicated by the superimposition of mood disorders. Episodic and chronic tension-type headache (TTH) and chronic facial pain may be associated with psychiatric comorbidity as psychiatric disorders may be present in many headache conditions<sup>10</sup>. A recent study<sup>11</sup> evaluated patients with different headache types and reported that depression was a frequent co-morbid condition, more specifically in those presenting chronic migraine (MIG). Depression is a clinical disorder commonly described by feelings of sadness, despair, emptiness or loss of interest or pleasure in activities in which others feel pleasure, satisfaction and interest<sup>12</sup>. More intense depression increases the likelihood that stress trigger a headache, increases headache pain severity and lead to a poorer response to treatment<sup>12</sup>. Significant associations between headache and depression have been observed in both chronic and clinically depressed populations<sup>13</sup>. Other affects, specifically anger, have also been discussed regarding its relationship to headache<sup>13</sup>. Anger is a state of displeasure ranging in intensity from mild irritation to intense fury in response to a perceived wrong that threatens the well-being of an individual or others with whom the individual identifies<sup>12</sup>. How the subject expresses or manages his or her anger can influence the course and outcome of disease and this affect has usually being classified in anger-in and anger-out<sup>12</sup>. Individuals with headaches are more likely to hold their anger-in, and they experience increased pain severity including headache. Their failure to express anger leads to more disability and increases the risk for experiencing more headache attacks, severer headache pain and more headache related disability. Studies have demonstrated that headache sufferers in general, have difficulties in regulating anger and they are more likely to turn their anger inward toward themselves<sup>14</sup>. In a study<sup>14</sup> in which migraine patients and control subjects were subjected to an anger provoking situation, those presenting migraine pain exhibited less anger behavior verbally and behaviorally, but more anger behavior was expressed somatically as compared to control individuals<sup>14</sup>. Anger turned inward may be a common factor predictive of headache<sup>14</sup>. Conflict with regard to anger or the expression of it, is the most commonly reported affective factor in headache individuals<sup>13</sup>. Even though, psychological factors have been investigated to a certain extent in headache sufferers, there is still scarcity of data regarding some psychiatric disorders in patients with BB and CMDs. Thus, the objective of this investigation is threefold:

1. Evaluate scores in hostility in different headache types in subjects with CMDs and BB;
2. Assess scores in depression in those different headache subgroups
3. Evaluate anger-in in CMDs and BB subjects with different headache types.

## **II. Material And Methods**

### **3.1 Sample**

The clinical charts of all patients (n=227) who sought diagnosis and treatment between January 2010 and January 2017 presenting accurate information about signs and symptoms of a specific type of headache were retrieved from a database and retrospectively reviewed comprehensively by a specialist in the field of CMDs and Orofacial pain (OFM). During clinical assessment, the principles of the Helsinki declaration were followed: Patients were informed that their clinical evaluation and use of questionnaires had no absolute risk for their health, that any physical or psychological discomfort warranted the discontinuity of the evaluation, that accurate and comprehensive evaluation was necessary in order to obtain accurate data and diagnosis before planning any treatment, that the principal examiner was scientifically experienced and qualified and that her or his data would provide practical clinical benefits in future studies and treatments. Patients signed a formal consent allowing the use of their clinical and demographic data for research purposes. All patients and controls were examined in the same period of time. The research involved a total of 227 clinical charts. There were 211 females and 16 males ranging in age from 11 to 75 years old and the average age of the

whole sample was about 36 years old. Controls (41 females and 13 males, mean age 36.3 years old, range= 18-56) were those individuals referred over the same period of time presenting no CMDs, no BB, no headache.

**3.1 Inclusion criteria for BB:** Patient's report of catching himself/herself clenching or grinding the teeth at daytime and or during the night, friends' and/or relatives' report of grinding the teeth at night, patient's report of fatigue in the masticatory muscles during the day following eating and/or speaking, awakening with facial, TMJ and/or TMJ pain, headache and/or dental pains and a report of jaw locking on awakening in the morning.

**3.2 Inclusion criteria for CMDs:** Presence of TMJ noises, pain on palpation of the TMJs and/or masticatory muscles, difficulties to perform normal jaw movements, a complaint of muscle and/or joint pain and seeking active treatment for CMDs.

**3.3 Inclusion criteria for TTH:** A report of bilateral pain in the temporal and/or frontal region, pain described as dull, steady, pressing or compressing, band-like type and moderate in intensity in both sides, a report of nausea (occasional), absence of vomiting, and presence of trigger points in the cervical and/or neck areas directly associated with referred pain to the anterior part of the head.

**3.4 Inclusion criteria for MIG:** Headache described as unilateral located anteriorly and laterally over the head, pain described as very intense, presence of nausea and/or vomiting, pulsating, photophobia and phonophobia and presence of ocular autonomic effects<sup>15</sup>.

**3.5 Inclusion criteria for combination headache (COMB):** Pain described as usually bilateral, very intense in one side, mild or moderate in the opposite side and with characteristics of common migraine in one side: very intense, pulsating and with ocular autonomic effects unilaterally and lasting hours and more usually days.

**3.6 Inclusion criteria for occipital neuralgia pain (ON):** Pain described in three anatomic areas (retroocular, anteriorly in the head and occipital + suboccipital), described as very intense presenting with nausea, vomiting, described as burning (sub-occipital area), pulsating and lancinating, intermittent and presenting with paresthesia in the occipital area, reports of dizziness, stuffiness of the ear, and constriction of the nose.

**3.7 Inclusion criteria for myofascial headache (MYOF):** Pain described anteriorly in the head, unilateral or bilateral, described as mild moderate or severe, steady, pulsating only when intense, usually associated with the presence of unilateral or bilateral trigger points in the neck and or cervical area, absence of characteristics of common migraine.

**3.8 Exclusion criteria:** Subjects and controls presenting with severe psychiatric disorders, difficulties to respond properly to questionnaires and presence of neuromuscular disorders: Parkinson's disease, other epilepsy type, speech and cognitive difficulties were excluded from the comprehensive initial examination and their charts were excluded.

### III. Measures

Cook-Medley instrument for hostility: Hostility is typically defined as a negative attitude towards others in general and encompasses a set of constructs including cynicism, anger, mistrust and aggression. This instrument is a 46-item true/false questionnaire derived the Minnesota Multiphasic Personality Inventory and used widely in epidemiologic studies. Beck Depression Inventory (BDI): The BDI is a 21-item, self-report rating inventory in which the participant selects an alternative in each question which defines how he/she is currently feeling about depression. Anger-in instrument: The instrument is a 29 self-report inventory assessing difficulties to express anger, anger taken inward and or expressed outwardly. The instrument was developed in the Orofacial Pain Department at UNIRG Dental School.

### IV. Statistical Analysis

Statistical analysis used in the current investigations included Fisher's exact test and Kruskal-Wallis followed by Dunn's multiple comparison test. A significant statistical difference was accepted if  $p < 0.05$ .

### V. Results

The current investigation evaluated scores in hostility, depression and anger-in in different subgroups of headache subjects with CMDs and BB as compared with a control group without BB and without CMDs. Age was not significantly different among the evaluated subgroups (Kruskal-Wallis' statistics with Dunn's test

p=0.30). Females predominated only when the subgroups TTH and Controls (Fisher's exact test  $p < 0.01$ ) and COMB and CONT (Fisher's exact test,  $p < 0.0004$ ), were compared. As for scores in hostility, there was a statistically and significant difference when the headache groups were compared (non parametric Kruskal-Wallis followed by Dunn's test,  $p < 0.0002$ ). However, significant differences were observed only when the subgroups TTH versus MIG ( $p < 0.05$ ), MIG versus CONT ( $p < 0.001$ ), and ON versus CONT ( $p < 0.05$ ), were compared. A significant statistical difference in depression scores was observed in the current investigation (Kruskal-Wallis's statistics and Dunn's multiple comparison test,  $p < 0.0001$ : TTH versus MIG ( $p < 0.001$ ); TTH versus ON ( $p < 0.05$ ); MIG versus MYOF ( $p < 0.05$ ); MIG versus CONT ( $p < 0.001$ ); COMB versus CONT ( $p < 0.01$ ); ON versus CONT ( $p < 0.001$ ); MYOF versus CONT ( $p < 0.05$ ). Regarding anger-in scores, a statistically and significant difference was found when the subgroups were compared (Kruskal-Wallis' statistics followed by Dunn's multiple comparison test  $p < 0.001$ ): TTH versus COMB ( $p < 0.05$ ); TTH versus MYOF ( $p < 0.01$ ); TTH versus CONT ( $p < 0.05$ ); MIG versus ON ( $p < 0.001$ ); MIG versus CONT ( $p < 0.001$ ); COMB versus ON ( $p < 0.001$ ); COMB versus CONT ( $p < 0.001$ ); ON versus MYOF ( $p < 0.001$ ). and MYO versus CONT ( $p < 0.001$ ).

## VI. Discussion

Scores in hostility in subjects with different headache types One of the objectives of the current study was to compare **scores in hostility** in individuals in different headache subgroups with those in the control one. Data showed that only those individuals in the **migraine (MIG)** and **occipital neuralgia (ON)** subgroups demonstrated statistically significant higher scores when compared to the TTH and Control subgroups. Because subjects presenting with TTH did not demonstrate higher scores in hostility as compared to control ones, this outcome is not in line with one study<sup>16</sup> asserting that TTH individuals are sensitive, somewhat resentful, rigid and hostile. Regarding migraine, one investigation<sup>17</sup> evaluated migraine, personality and psychiatric comorbidity and described migraine patients as anxious, hostile, resentful and rigid, thus, supporting data in the current research. Reports in the literature<sup>18</sup> have associated migraine with a wide variety of psychiatric and somatic disorders and such patients have been shown to score significantly higher than controls on indices of aggression and hostility. of the literature, researchers<sup>19</sup> reported that migraineurs have usually been described as hostile, unable to express anger, presenting with rigid superego, intolerance to frustration, with feelings of resentment, rigidity and inflexibility. Negative affect consisting of anxiety, anger and depression is only one of some psychological factors which antecede the development of headache including migraine<sup>19</sup>. It may be that because occipital neuralgia and migraine headaches have been described as very intense and present problems with diagnosis and management, they become more chronic, occur more frequently and become recalcitrant to treatment. Studies<sup>20</sup>, have reported that those who experience some chronic headaches suffer from less openness about feelings, greater instability, increased irritability and hostility. Occipital neuralgia has usually been described as a very intense, protracted, intermittent, unbearable headache pain which may be confused with migraine. It may be that such characteristics cause irritability, hostility and despair in ON sufferers. Personality disorders contributing to refractoriness to treatment may cause frustration in the health provider as well as in the patient<sup>21</sup>

### 4.1 Scores in depression

**The second objective** of the current study was to compare scores in depression in headache sufferers and control individuals. Higher scores in depression were observed in all subgroups presenting headache as compared to control individuals. Thus, the outcome of the current study concurs with a previous investigation<sup>22</sup> reporting that headache patients are described as mildly anxious, but depressed relative to their non headache counterparts. Depression is a common disorder observed in headache patients and 5 a 10% outpatients have major depression<sup>23</sup>, thus the prevalence of depression is very high in those individuals presenting to primary care physicians with complaints of headaches<sup>23</sup>. Headache patients are more likely to suffer from anxiety and depression<sup>20</sup>. Headache, depression and other neurophysiological disorders occur very commonly in outpatient populations<sup>9</sup> and patients with depression are more vulnerable to present many complaints particularly head and neck pain<sup>24</sup>. In the current investigation in different headache subgroups, the highest means in depression were observed in the subgroups complaining of migraine and ON as compared to the other headache subgroups. It may be that more intense, frequent pain of longer duration together with significant psychopathology including severe hostility inward and abuse of medication in migraine and ON patients may contribute at least in part for more intense depression and anxiety. In this regard, one study<sup>25</sup> describes migraineurs as those presenting higher scores in neuroticism, anxiety and aggression taken inward which is directly associated with depression. It may be that depression in migraineurs is associated with severer psychopathology including a history of maltreatment during childhood<sup>26</sup>. Patients suffering from pain syndromes, especially chronic ones, have an even higher prevalence of depression<sup>23</sup>. Depression is present in almost 80% of migraineurs<sup>9</sup>, but it is very likely that a subgroup of migraineurs present with higher scores in depression.

Excessive use of triptans, over-the counter medication, and analgesic opioids used for more than three months may result in medication-overuse headache<sup>27</sup> and there is no doubt that such a behavior may contribute with depression. Excessive medication to alleviate symptoms has been traditionally considered a risk factor for poor migraine prognosis. Those who take analgesics excessively are more likely to develop frequent headaches<sup>28</sup>. One study<sup>29</sup> did not investigate psychopathology in headache patients, but found that severer clinical and autonomic symptoms were observed in those patients presenting with migraine and ON as compared to TTH ones. Further support for the previous assumption comes from one study<sup>19</sup> reviewing the literature about mood disorders and migraine, reporting that even though negative mood was common to other headache groups, migraine was closely related with depression that correlated with headache intensity. Additionally, negative emotions in headache sufferers including anxiety, anger and depression may increase linearly with the frequency of headaches<sup>19</sup>. Higher scores in fear of expressing anger which may then become depression, predominate in patients with severe migraine<sup>19</sup>. In the present investigation, higher scores in depression were observed in those subjects presenting migraine as compared to those complaining of TTH. This outcome is supported by one investigation<sup>29</sup>, reporting that relative to chronic TTH, patients with chronic migraine were more likely to have depressive and anxiety symptoms. When migraineurs are compared with other subgroups of pain patients, they are more likely to present depression, drug abuse and suicide attempt<sup>21</sup>. In migraine patients a repressed affect is maintained in a latent state in the form of rage<sup>30</sup>, thus, both anger and rage becomes depression. Further, the greater the amount of repressed anger, the higher the level of depression. ON and depression ON is considered a neuropathic intense, protracted, intermittent, unbearable, chronic pain<sup>30</sup>. It is very likely that its intensity, frequency, diagnostic and refractoriness to therapeutic intervention<sup>31</sup> lead patients to become irritated, frustrated and depressed. One study<sup>32</sup>, described a case of ON presenting with concomitant depression according to the BDI, and reported that following transcutaneous electrical stimulation with implanted electrodes, both depression and clinical symptoms improved significantly. ON patients may have problems with depression, multiple treatments and excessive medication use<sup>33</sup>. ON is a severe lancinating, protracted headache pain and the association between chronic pain and depression has been well established. Mood disorders significantly influence the effectiveness of treatment modalities for chronic pain. Depression is mostly associated with psychiatric conditions including mood disorders and anxiety<sup>34</sup>. Recalcitrant ON may be associated with significant depression which may improve following the use of an implanted electrical stimulation unit<sup>32</sup>. Scores in anger inward in different headache types Another goal of this investigation was to compare means in anger held inward in different groups when compared to the control subgroup. In the current study, means in anger-held inward in TTH, migraine, combination headache and myofascial headache were higher, different and statistically significant when compared to the control group. The highest scores in anger held inward were observed in those subgroups presenting migraine, combination headache and myofascial headache. Because scores in hostility and anger held inward were lower in TTH as compared to migraine headache patients, the outcome of this investigation is not in line with one study<sup>35</sup> reporting that psychiatric comorbidity is higher in TTH than in migraine patients. It may be that subgroups of migraine, combination headache and myofascial headache individuals present a psychological make up in which psychosomatic disorders predominate, and many of those individuals hold anger inward. In this regard, it has been reported<sup>14</sup> that almost 20% of people suffering of recurrent headaches present with psychosomatic disorders and many headache sufferers do have problems regulating anger. Somatization occurs in these headache sufferers when they have feelings of love mixed with rage and guilt about the rage. Turning anger inward makes these individuals more vulnerable to develop headache symptoms<sup>14</sup>. Myofascial headache individuals presented scores in anger held inward that were identical to those presenting with migraine and combination headache. Germaine to this issue is one study<sup>36</sup>, arguing that muscular pain headaches can also be part of unspecific somatic manifestations. Regarding higher scores in anger held inward in migraine, combination headache and myofascial headache sufferers, the results of the current investigation are in line with a previous study<sup>18</sup>, indicating that the predominant personality in migraine sufferers is repressed hostility, unexpressed anger, intolerance to frustration and feelings of resentment. Moreover, anger held inward and depression increase linearly with the frequency of headaches<sup>19</sup>. In the current study, TTH sufferers demonstrated higher and statistically significant different scores in anger held inward as compared to control subjects. Thus, this outcome concurs with one investigation<sup>37</sup>, demonstrating that TTH individuals have significantly scores in anger-in as compared to control ones and keep their angry feelings to themselves rather than expressing them.

## **V. Conclusions**

All headache subgroups presented with higher scores in hostility. However, the highest scores in hostility were observed in the migraine and occipital neuralgia subgroups. Subjects in these headache subgroups usually present higher pain scores. Using the Beck depression and a novel instrument to measure anger-in, all headache groups in the current study demonstrated higher scores in depression and anger-in. Thus, headache subjects with bruxing behavior and TMDs, are characterized by higher scores in hostility, depression and anger-

in. Future studies should evaluate a putative relationship between intensity of pain, hostility, depression and anger-in in headache subgroups with BB and TMDs.

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**Table 1:** Social and demographic data in craniomandibular disorder and bruxer subjects presenting with different headache types and control non headache individuals.

Craniomandibular Disorders and bruxers												
Headaches	TTH=100		MIG=17		COMB=41		ON=27		MYOF=42		CONT=54	
GENRE	n	%	n	%	n	%	n	%	n	%	n	%
Females	92	92	16	94.1	41	100	25	92.6	37	88	41	75.9*
Males	8	8	1	5.9	0	0	2	7.4	5	12	13	24.1
Totals	100	100	17	100	41	100	27	100	42	100	54	100
Mean Age	32		37.2		37.6		39.1		34.2		36.3**	
SD	11.5		11.8		12.1		12.8		10.7		10.9	
Range	11-54		18-61		18-59		20-75		14-63		18-56	

\*Fisher’s exact test: Females predominated in the group with TTH headache as compared with the control group (p<0.01). Females predominated in the combination headache group as compared with the control one (Fisher’s exact test p<0.0004)

\*\*Kruskal-Wallis and Dunn’s test p=0.30

**Table 2:** Scores in hostility in CMDs and BB patients with different headache types and in control subjects.

Craniomandibular Disorders and BB						
HeadacheTypes	TTH	MIG	COMB	ON	MYOF	CONT
	100	17	41	27	42	54
Hostility						
Mean	18.5	21.3	18.7	20.0	18.6	16.8*
SD	4.8	3.6	6.5	4.7	4.6	4.9
Range	7-34	12-29	6-33	11-30	8-29	4-29

\*Kruskal-Wallis statistics p<0.0002: TTHS versus MIG (p<0.05); MIG versus CONT (p<0.001); ON versus CONT p<0.05).

**Table 3:** Scores in depression (BDI) in CMDs and BB patients with different headache types and in control subjects

Headache types	TTH	MIG	COMB	ON	MYOF	CONT
Depression						
Mean	10.0	19.6	13.1	14.9	11.8	6.6*
SD	6.2	8.2	8.7	6.7	6.9	6.3
Range	0-29	5-30	0-41	3-35	0-34	0-23

\*Kruskal-Wallis Statistics p<0.0001: TTH versus MIG (p<0.001), TTH versus ON (p<0.05), MIG versus MIOF (p<0.05), MIG versus CONT (p<0.001), COMB versus CONT (p<0.01), ON versus CONT (p<0.001), MYOF vs CONT (p<0.05).

**Table 4:** Scores in anger-in in CMDs and BB patients with different headache types and in control subjects.

Craniomandibular Disorders and BB						
Headache Types	TTH	MIG	COMB	ON	MIOF	CONT
Anger-in						
Mean	118	141	140	93.3	139.3	84.6*
SD	40.5	55.8	33.0	35.6	9.9	46.7
Range	30-238	38-212	22-228	5-210	0-246	17-165

\*Kruskal-Wallis test p>0.001: TTH versus COMB (p<0.05), TTH versus MYOF (p<0.01), TTH versus CONT (p<0.05), MIG versus NO (p<0.001); MIG versus CONT (p<0.001); COMB versus NO (p<0.001), COMB versus CONT (p<0.001), NO versus MYO (p<0.001), MYO vs CONT (p<0.001).

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