**Method Article – Title Page**

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| **Title** | *Calculating Medication Load for Patient Analyses in Neuroimaging* |
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**ABSTRACT**

Psychiatric medications present a unique problem for neuroscience, particularly functional magnetic resonance imaging (fMRI) analyses, as many medications can influence neural activity in various brain regions. Recruiting participants that are medication-free may bias experimental samples, while removing participants from current medications can not only be dangerous and ethically problematic, but it may also result in momentary increases in symptomatology (not to mention other negative side-effects). To complicate things further, psychiatric patients are generally prescribed multiple, divergent types of medications (e.g. antidepressants in combination with anxiolytics, etc.) all with variations in dosages. Accounting for these differences and their influence on neuroimaging data is complicated. To account for these differences, we propose to calculate an overarching index of medication load, which can be used as a covariate or regressor in various control style analyses.

* A proposed methodology to calculate participant specific index of medication load.

**SPECIFICATIONS TABLE**

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| **Subject Area** | Neuroscience |
| **More specific subject area** | *Clinical Neuroscience* |
| **Method name** | *Medication Load Index Calculation* |
| **Name and reference of original method** | *Olié E, Doell KC, Corradi-Dell’Acqua C, Courtet P, Perroud N, Schwartz S (2018): Physical pain recruits the nucleus accumbens during social distress in borderline personality disorder. Soc Cogn Affect Neurosci. 13: 1071–1080.* |
| **Resource availability** | *If applicable, include links to resources necessary to reproduce the method (e.g. data, software, hardware, reagent)* |

**\*Method details**

Medication Load Calculation protocol:

In order to develop a protocol for calculating overarching medication load, we combined techniques and procedures from various sources in order to create a coherent marking schema. To do so, all dosages are first coded as absent (0), low (1), or high (2) for each medication separately (Table 1). For antidepressants, we utilized a previously employed approach (Sackeim, 2001) that differentiates between 4 levels of dosages, which are then converted into low-dose (levels 1 and 2) and high-dose (levels 3 and 4). For antipsychotic treatments, the doses are first converted into chlorpromazine dose equivalents, and coded as 0, 1, or 2, for no medication, up to mean effective daily dose, or above the daily dose respectively, as defined by Davis and Chen (2004). Other medications (labelled as “miscellaneous” in Table 1 and 2) including anxiolytics (e.g. lorazepam) and psychostimulants (e.g. methylphenidate) doses are coded as 0 for absent, and 1 if present, because these medications tend to be prescribed at the lowest dosages. Finally, to generate a composite measure of total medication load index, reflecting dose and variety of different medications taken, each category and all medication codes are summed for each individual participant (examples are shown in Table 2).

Medication Load as a covariate:

There are multiple analyses that can be utilized to investigate the overarching influence of medication on neuroimaging data in patient studies. For example, the medication load can be entered as a correlate or regressor into statistical models inside of fMRI analyses, alongside any other relevant factors (e.g. age). If this process is used, we recommend doing so, only in the case where the analysis does *not* compare patients with healthy controls. In general, control participants are un-medicated (which is why they are controls), and so entering a covariate that is all 0s for one group, and contains more variance (e.g. ranging from 0 to 5 or 6) in another group would likely capture the majority of variance that is attributable to group differences in general and not solely related to medication. Rather, utilizing this type of analysis in cases where researchers are comparing multiple patient populations (e.g. borderline patients compared to bipolar patients), each with similar types and variations in medications is suggested.

Additionally, medication load can be utilized in separate additional analyses (e.g. supplementary analyses/materials) by extracting the underlying signal from significantly activated brain regions (e.g. by utilizing a region of interest approach). Similar to the previous example, these analyses should also be conducted *within* the patient group (or between multiple medicated patient groups), and not between patients and controls. More specifically, to test for any effects of Medication load on significantly activated brain regions measured utilizing fMRI, simple correlations (i.e. Spearman’s correlations) or analyses of covariance (ANCOVAs) can be computed using beta estimates extracted from significantly activated brain regions (e.g. Doell et al., in press.; Olié et al., 2018). Specifically identifying significant interactions that include medication load (e.g. Medication Load x Factor 1), or simply main effects would suggest that there is an effect of overall medication load in contributing to the variation in the underlying brain signal in that region.

Limitations of this approach:

The limitations of utilizing such an approach should also be clearly stated. This medication load technique can allow researchers to investigate the broad influence that psychiatric medications might have on influencing various data, but it would not allow for the specific claim “medication had no effect”. This analysis is proposed as an imperfect control and additional analysis tool, which can be utilized when there is no other feasible investigation possible.

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| **Table 1:** Popular Medications and their relevant dosage ranges according to each level of medication load (i.e. absent, low, and high) | | | | |
|  | **Medication Load Level:** | **absent (0)** | **low (1)** | **high (2)** |
|  | Corresponding Dosage Range (mg/day) | | |
| **Antidepressants** | Citalopram, Escitalopram, Fluoxetine, Paroxetine | 0 | 1-19 | ≥20 |
| ﻿Sertraline | 0 | 1-99 | ≥100 |
| Venlafaxine | 0 | 1-224 | ≥225 |
| Duloxetine | 0 | 1-59 | ≥60 |
| ﻿Amitriptyline, imipramine,  desipramine, trimipramine, clomipramine, maprotiline, doxepin, nomifensine | 0 | 1-199 | ≥200 |
| Mirtazapine |  | 1-29 | ≥30 |
| **Antipsychotics** | Quetiapine | 0 | 1-49 | ≥50 |
| Olanzapine | 0 | <10 | ≥10 |
| Risperidone | 0 | <2 | ≥2 |
| Aripiprazole | 0 | <1.5 | ≥1.5 |
| Amisulpride | 0 | 1-49 | ≥50 |
| **Miscellaneous** | Methylphenidate | 0 | If present | NA |
| Trazodone | 0 | If present | NA |
| Benzodiazepines | 0 | If present | NA |
| Zolpidem, zopiclone | 0 | If present | NA |

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| **Table 2:** Example medications prescribed and their corresponding loads (shown in grey) for antidepressants, antipsychotics, and other miscellaneous prescriptions (e.g. anxiolytics, and psychostimulants). | | | | | | | | |
|  | **Antidepressant** | | **Antipsychotics** | | | **Miscellaneous** | | **TOTAL MEDICATION LOAD**  **INDEX** |
| Participant | Original (dosage mg/d) | Load | Original  (dosage mg/d) | Chlorpromazine equivalent (mg/d) | Load | Original  (dosage mg/d) | Load |
| 1 |  | **0** |  |  | **0** |  | **0** | **0** |
| 2 |  | **0** |  |  | **0** | Methylphenidate (20) | **1** | **1** |
| 3 | Citalopram (10) | **1** |  |  | **0** |  | **0** | **1** |
| 4 |  | **0** |  |  | **0** | Methylphenidate (20) | **1** | **1** |
| 5 | Citalopram (20) | **2** |  |  | **0** |  | **0** | **2** |
| 6 | Fluoxetine (20) | **2** |  |  | **0** |  | **0** | **2** |
| 7 | Venlafaxine (225) | **2** |  |  | **0** |  | **0** | **2** |
| 8 | Fluoxetine (20) | **2** |  |  | **0** |  | **0** | **2** |
| 9 | Fluoxetine (60) | **2** |  |  | **0** | Trazodone (100) | **1** | **3** |
| 10 | Fluoxetine (20) | **2** |  |  | **0** | Oxazepam (1) | **1** | **3** |
| 11 | Venlafaxine (150) | **2** | Quetiapine (25) | 25 | **1** | Oxazepam (1) | **1** | **4** |
| 12 | Fluoxetine (20) | **2** | Quetiapine (25) | 25 | **1** | Oxazepam (1) | **1** | **4** |
| 13 | Fluoxetine (20) | **2** | Quetiapine (50) | 50 | **2** |  | **0** | **4** |
| 14 | Fluoxetine (40) | **2** | Olanzapine (5) | 100 | **2** | Methylphenidate (40) | **1** | **5** |
| 15 | Fluoxetine (40) | **2** | Quetiapine (200) | 200 | **2** | Mirtazapine (7.5) | **1** | **5** |

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**Declaration of interests:**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**\*References:**

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