**Mismatch negativity and P3a in drug-naïve adults with attention-deficit hyperactivity disorder**

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**Supplementary Methods, Tables (S1, S2) and Figures**

**Behavioral Measures**

***The Chinese version of the Swanson, Nolan, and Pelham, version IV scale (SNAP-IV).***The participants reported their ADHD-related symptoms on the SNAP-IV (Swanson *et al.*, 2001), which is a 26-item scale rating on a 4-point Likert scale with a score of 0 for "not at all," to 3 for "very much." There are 18 items parallel to the core symptoms of DSM-IV ADHD (Items 1-9 for inattention symptoms; Items 10-18 for hyperactivity/impulsivity symptoms), and 8 items (Items 19-26) based on the DSM-IV of oppositional defiant disorder symptoms. The psychometric properties and norm of the parent (Gau *et al.*, 2008a) and teacher reports (Gau *et al.*, 2009) on the Chinese SNAP IV have been established, showing the same 3-factor structure as its English version (Gau *et al.*, 2008a). The SNAP-IV has been used for adults to report their ADHD-related symptoms (Yang *et al.*, 2013). The Chinese SNAP-IV has been widely used in clinical and research settings in Taiwan regarding treatment studies (Chou *et al.*, 2009, Gau *et al.*, 2008b, Gau & Shang, 2010), epidemiological studies (Chen *et al.*, 2015, Chen *et al.*, 2017, Chen *et al.*, 2019, Gau *et al.*, 2008a, Gau *et al.*, 2009, Tsai *et al.*, 2017), and clinical studies (Chen *et al.*, 2015, Chiang *et al.*, 2015, Chiang *et al.*, 2016, Chiang & Gau, 2016, Chiang *et al.*, 2019, Chiang & Gau, 2008, Chien *et al.*, 2014, Liu *et al.*, 2011, Shang *et al.*, 2015, Shang *et al.*, 2013, Tsai *et al.*, 2013, Yang *et al.*, 2013). The participants only reported their ADHD symptoms, i.e., inattention and hyperactivity-impulsivity, on the first 18 items of the SNAP-IV. In this study, we only include the first 18 items of the SNAP-IV in the clinical report form.

***The Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000).*** The BRIEF is an 86-item questionnaire reported by adults aged 18 and older. The BRIEF is developed to evaluate daily-life or real-world behaviors related to [executive function](https://en.wikipedia.org/wiki/Executive_function)s for adults to report on themselves (Baron, 2000). The BRIEF measures are comprised of eight clinical subscales which are collapsed into two broad indices: (1) Behavioral Regulation Index (BRI); Inhibit, Shift and Emotional Control; and (2) Metacognition Index (MCI): Initiate, Working Memory, Planning and Organizing, Organization of Materials, and Monitor; as well as an overall index (Global Executive Composite, GEC). The items are rated on a frequency level (1 for "Never," 2 for "Sometimes," and 3 for "Often"). The BRIEF has been reported to have excellent psychometric properties, including high test-retest and interrater reliability, as well as face and predictive validity (Baron, 2000). The Chinese version of the BRIEF has been used in epidemiological (Tsai *et al.*, 2019) and clinical (Goto *et al.*, 2017) research.

**Neurocognitive tasks**

***Conner's Continuous Performance Test (CCPT)***.

The CCPT is a 14-minute, widely-used computerized task for individuals aged 6 and up (Conners & Staff, 2000). It is a non-X type CPT test of go/no-go paradigm, which requires subjects to tap on the spacebar when any character except *X* is shown on the screen (Conners & Staff, 2000). There are six blocks in CCPT, with three sub-blocks each containing 20-letter presentations, resulting in 360 trials in total. The 360 trials, composed of 10% no-go targets, were presented with six blocks and three sub-blocks (20 trials in each sub-block). The sub-blocks differ in Inter-Stimulus Intervals (ISIs) of 1, 2, and 4 seconds, and the sequence of ISI conditions is presented randomly. Seven indexes are presented in this study to address the three attention profiles proposed by Egeland and Kovalik-Gran (Egeland & Kovalik-Gran, 2010): (1) focused attention: omission errors, reaction time (RT) variability, Hit RT standard errors (SE); (2) cognitive impulsivity: commission errors, perseverations (defined as the responses occurring less than 100 ms following the stimuli that are too quick for a respondent to react); and (3) vigilance: Hit RT and Hit RT SE changed across different ISIs (i.e., slower and more variable RT with more extended ISI changes).

**Cambridge Gambling Test (CGT)** CGT is one of the tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd), which is a set of computerized tests to examine nonverbal neuropsychological functions. CGT is designed to assess decision-making capabilities (Rogers *et al.*, 1999), while the participant is presented with ten boxes, colored either red or blue, and appeared in varying ratios (6:4, 7:3, 8:2, 9:1) of red to blue. They are informed that a yellow token is hidden in one of the boxes. At the bottom of the screen are two response boxes, one for each color. The participant must use such information to guess whether the token is hidden under a red or blue box. If the participant had located the hidden token correctly, then the points they wagered were added to their total score. If they had made the wrong decision, however, then that the same amount was subtracted from their total. Participants were always able to see their point total on the screen. They were able to select their bets from a list of five options calculated by the computer, with the amounts corresponding to 5%, 25%, 50%, 75%, and 95% of their current point total. These bet amounts were presented either in ascending or descending order during CGT administration (ascending and descending conditions). Participants were required to choose a wager from any of these possible amounts within 2 sec. If they failed to do so, then the last bet was automatically set by the computer. Their bets were presented together with a sound, with low-pitched tones indicating low bets, and high-pitched tones indicating high bets. This work shows six indexes: (1) Overall bet proportion: both the ascending and the descending conditions, (2) Risk adjustment: the mean risk-taking score (points) for each box ratio for both the ascending and the descending conditions where points to gamble differ relative to box ratio, and (3) Risk-taking: the total difference between risk-taking scores (points gambled) in the ascending and descending conditions (delay aversion).

**Auditory event-related potentials (ERP) method**

**ERP recording environment**

We followed the standard protocols of the passive auditory oddball paradigm (Duncan *et al.*, 2009, Light *et al.*, 2010) at our lab, which had been used in our previous research (Hsieh *et al.*, 2019, Hsieh *et al.*, 2012, Huang *et al.*, 2018, Lin *et al.*, 2014, Lin *et al.*, 2012). Audiometry testing was performed before ERP recording to exclude subjects who could not detect 40-dB sound pressure level tones at 500, 1000, and 6000Hz presented to either ear. Auditory stimuli were presented binaurally by foam insert headphones. The stimuli were generated by, and data was recorded by Neuroscan STIM and ACQUIRE system [Neuroscan, El Paso, Tex.]. Electrodes were used at 32 recording sites utilizing Neuroscan QuikCaps (According to QuikCap website: All electrodes were placed according to the International 10-20 electrode placement standard). Electrodes placed at the tip of the nose and Fpz served as the reference and ground, respectively. Four additional electrodes placed above and below the left eye and at the outer canthi of both eyes are used for monitoring blinks and eye movements. All impedances would be below 5 kΩ. Signals were digitized at a rate of 1 kHz with system acquisition filter settings of 0.5 to 100 Hz, with no 60Hz notch filter.

**MMN/P3a session**

 ERP data were collected while participants viewed a benign cartoon film while the cartoon soundtrack was turned off and replaced by the experimental tones. To minimize eye movement and muscle artifact during the recording, the cartoon film is presented at eye level on a 19-inch LCD monitor screen. A duration-deviant auditory oddball paradigm was employed, as standard (p = 0.90, 50-ms duration) and deviant (p = 0.10, 100-ms duration) tones were presented in pseudorandom order with at least 2 standards are presented before each deviant. All stimuli were 1,000 Hz and 80dB with 1 msec rise-fall time and presented at a fixed 500msec onset-to-onset asynchrony. During the passive auditory paradigm, subjects were closely observed through a video monitor. They would be monitored visually and by EEG for signs of sleep or slow-wave activity, which, if present, prompted the experimenter to speak briefly with the subject. In addition, online ERP averages to standard and deviant tones were also collected to monitored signal quality and the number of sweeps free of gross artifacts (defined as ±100 μV across the 100~500 msec following stimuli). EEG acquisition was terminated when a minimum of 225 artifact-free deviant trials were collected, while the whole session took over approximately a 30min period.

**Offline data processing**

Offline data processing was performed with automated procedures utilizing Neuroscan Scan 4.5 software blind to clinical group in the following ways: (1) continuous recordings were mathematically corrected for eye movement artifact using established methods (Semlitsch *et al.*, 1986); (2) digital bandpass filtering within 1 to 40 Hz; (3) continuous data were divided into epochs relative to the onset of stimuli within −100 to 500 milliseconds range; (4) automatic removal of artifacts by excluding the epochs containing amplitude differences of ±50 μV in frontal recording sites; (5) construction of the MMN/P3a waves by subtracting the averaged standard ERP from each of the averaged deviant ERP; (6) the resultant MMN subtraction waveforms were lowpass filtered at 20 Hz (phase shift and 24dB/octave roll-off) to remove residual high-frequency artifact; (7) individual scoring of maximum MMN amplitudes between 90 and 250 msec and of maximum P3a amplitude between 210 and 350 msec. MMN and P3a amplitudes were assessed from the midline electrodes Cz for analysis (Duncan *et al.*, 2009, Rydkjaer *et al.*, 2017).

**Supplementary Table S1.** Pearson's correlations between age and MMN/P3a parameters.



**Supplementary Table S2.** Lasso method for MMN amplitude in ADHD

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **DF** | **Estimate** | **Cross-validation estimate** |
|  |  |  | 1 | 2 | 3 | 4 | 5 |
| Intercept | 1 | -2.152 | 0.0383 | -0.0440 | -0.123 | -0.0177 | 0.0996 |
| Metacognition Index | 1 | 0.006 | 0.1990 | 0.5111 | 0.680 | 0.4398 | 0.6808 |
| Hit reaction time: inter-stimulus intervals | 1 | -0.817 | -0.6364 | -0.5181 | -0.212 | -0.1938 | -0.3992 |
| Cambridge gambling task: risk adjustment | 1 | 0.133 | 0.0833 | 0.0622 | 0.416 | 0.3398 | -0.0211 |

**Supplementary Figure**

Associations between MMN and behavioral parameters in the ADHD and control groups, corresponding to Table 3.

|  |  |
| --- | --- |
| **ADHD:** Cz MMN amplitude vs. Inattentive*r*=0.117, *p*=0.409 | **ADHD:** Cz MMN amplitude vs. Overall proportion bet (Descending) |
| **ADHD:** Cz MMN amplitude vs. Metacognition Index  | **Controls:** Cz MMN amplitude vs.  Risk adjustment (Ascending) |
| **ADHD:** Cz MMN amplitude vs. Hit reaction time ISI  | **Controls:** Cz MMN amplitude vs.  Risk adjustment (Descending) |
| **ADHD:** Cz MMN amplitude vs. Hit standard error changed by ISI | **Controls:** Cz MMN amplitude vs.  Risk taking (Descending) |

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