Supplementary Table. Neurophysiological Studies of Corollary Discharge dysfunction in schizophrenia

| STUDY | BACKGROUND | METHODOLOGY | KEY FINDINGS WITH IMPLICATIONS |
|-------|------------|-------------|-------------------------------|
| Zheng et al., 2015 | Premise ➤ Understanding neural functioning under Octave illusion could further understanding of AVH in SCZ ➤ Because of CD dysfunction in SCZ, under octave illusion, activation patterns from frontal to temporal areas differ between HC and SCZ | Methods ➤ Location: Hangzhou, China ➤ Sample: SCZ (first episode with AVH)=23, HC=23 ➤ Instructions: The participants were asked to focus on a white cross mark displayed on a computer screen of black background at 1 m distance from them. The paradigm was administered through earphones. Three minutes of silence preceded the administration of two sequences of octave illusion, separated by a gap of 10 sec from each other. ➤ Deutsch Octave Illusion ERP Paradigm Details – Two tone of 400 Hz and 800 Hz presented to either ear at a time together in a manner when the right ear received the high tone, the left ear received the low one, and vice versa. After first presentation, the auricular inputs were reversed for the second presentation such that each ear alternately received each of the 400 Hz and 800 Hz sequence. The tones were of 70 dB sound pressure level | Results ➤ Task-related theta power change values of frontal and temporal areas were significantly lower for both HC and SCZ groups with no between group difference ➤ Values of the task-related theta coherence difference between the ipsilateral frontal-temporal areas were increased in SCZ group ➤ Negative correlation between task related power changes in between the hemispheres ➤ Task related coherence differences in the right hemisphere positively correlated with hallucination scores of SCZ participants |

Implications ➤ Increased ipsilateral synchronization in SCZ during octave illusion is similar to activation patterns during AVH. This stronger mobilization or disinhibition implies a monitoring deficit. ➤ In SCZ the frontal area monitoring of the temporal part was not powerful enough, even if the synchronized pathway was ‘over-mobilized’, accounting for corollary discharge dysfunction hypothesis ➤ the dysfunctional right hemisphere linked to the corollary discharge might result in a relatively active left hemisphere, which is often the case
and 250 ms sine waves at equal amplitude and followed each other without pause.

| (Ford et al., 2014) | Premise | Methods | Result |
|---------------------|---------|---------|--------|
| Motor acts are preceded by efference copy of plan of execution which facilitates CD of the expected sensation in sensory cortex even when the causal chain between the act and its sensory consequence is indirect and dependent on external devices. | **Location**: California, USA  
**Sample**: SCZ=26, HC=22  
**Instructions**: During button tone condition, the participants were asked to deliver tones to themselves in the self-paced manner they were trained at. In the Pay tone condition they listened to the tone play back.  
**ERP Paradigm**: Participants pressed a button, every 1–2 seconds, to deliver 1000 Hz, 80 dB sound pressure level, tones with zero delay between press and tone onset (Button Tone). After 100 tones had been delivered, the task was stopped. The temporal sequence of tones was preserved for play back (Play Tone). In addition, subjects pressed a button at approximately the same pace, and no sound occurred (Button Alone). | **HC** had larger Lateralized readiness potential (LRP) – a measure of motor plan – preceding button press for tone delivery and N1 suppression than **SCZ**  
**Positive correlation between LRP amplitude and N1 suppression across both the groups** |
| For an ongoing hallucination in schizophrenia |

| (Nawani et al., 2014) | Premise | Methods | Result |
|----------------------|---------|---------|--------|
| CD dysfunction in SCZ evidenced as inadequate N100 suppression  
tDCS causes adaptive | **Location**: Karnataka, India  
**Sample**: SCZ=05  
**ERP Paradigm**: The Talk-Listen Paradigm as described by Ford et al., | **Before tDCS, N1 amplitude of Talk condition didn’t significantly differ from N1 amplitude of Listen condition; post tDCS this difference was significant.** |

Implication
- Even when efference copy is indirectly related to the sound associated with it and the sound does not strictly come from “self” **SCZ** exhibit efference copy and CD dysfunction
- Pre-movement activity reflects the efference copy
- Self-delivery of tones also produces robust N1 suppression and involves auditory cortex
- Using this paradigm CD mechanism can be studies in lab animals. Neurophysiological recordings used with lab animals and humans are comparable, making both the ‘talk’ and ‘button press’ paradigms and the physiological assay translatable across species
neuromodulation of N100

**Aim**
- Examining effect of tDCS in corollary discharge dysfunction in SCZ with AVH

2010. Talk condition: Participants made short crisp vocalizations of the phoneme “ah” repeatedly in a self-paced manner, about every 1–2 s, for 100 s. This speech was recorded using a microphone connected to the stimulus presentation computer and transmitted back to subjects through headphones in real time (zero delay).

Listen condition: The recording from the Talk condition was played back, participants had simply listen to it.

**Intervention**: Add-on tDCS therapy

**Implication**
- Add-on tDCS therapy was observed to modify and correct corollary discharge dysfunction in SCZ participants with AVH
- Neuroplasticity modulating effects of tDCS address auditory processing deficits in SCZ

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(Ford et al., 2012)

**Aim**
- CD dysfunction in SCZ is manifested as inability to distinguish self from externally generated experience
- To examine if CD dysfunction is specific to SCZ by exploring it in other psychotic illness and first degree relatives of psychotic patients
- To examine if reduced N1 suppression during talking is an endophenotype of

**Premise**
- CD dysfunction in SCZ is manifested as inability to distinguish self from externally generated experience

**Methods**
- **Location**: Chicago, USA
- **Sample**: SCZ = 30, SA = 19, BPP = 39, HC = 43, SCZ Relatives = 30, SA Relatives = 23, BPP Relatives = 50
- **ERP Paradigm**: The Talk-Listen Paradigm. Talk condition: Participants made short (<300ms), sharp vocalizations of the phoneme “ah” repeatedly in a self-paced manner, about every 1–2 s, for 180 s. This speech was recorded using a microphone connected to the stimulus presentation computer and transmitted back to subjects through headphones in real time (zero delay).

**Result**
- Inadequate N1 suppression in SCZ, SA and BPP group of psychotic patients
- N1 suppression failure among the patient groups didn’t correlate with current positive symptoms; though the patients group differed in degree of psychotic symptoms they didn’t in N1 suppression
- N1 suppression among first degree relative didn’t differ significantly from HC or probands

**Implication**
- Efference copy / CD dysfunction as reflected in failure of N1 suppression can be observed in SCZ and other psychotic disorders; it could be a trait marker for psychosis
- N1 suppression is not a robust endophenotype for psychosis risk nor is it a heritable trait in the family
| (Perez et al., 2012) | **Premise** | **Methods** | **Result** |
|---------------------|-------------|-------------|------------|
| CD dysfunction in SCZ is manifested as inability to distinguish self from externally generated experience. | **Location:** Chicago, USA  
**Sample:** CHR = 40, ESCZ = 41, HC = 86  
**ERP Paradigm:** The Talk-Listen Paradigm. Talk condition: Participants made short (<300ms), sharp vocalizations of the phoneme “ah” repeatedly in a self-paced manner, about every 1–2 s, for 180 s. This speech was recorded using a microphone connected to the stimulus presentation computer and transmitted back to subjects through headphones in real time (zero delay). Listen condition: The recording from the Talk condition was played back, participants had simply listen to it. | Inadequate N1 suppression in SCZ and ESCZ  
N1 suppression abnormalities are not affected by illness duration.  
No significant age effects were observed over N1 suppression from adolescence into adulthood.  
CHR group could not be statistically distinguished from either the HC or ESCZ groups.  
Attenuated speech-related N1 suppression was not related to positive or negative symptoms in early illness or CHR patients. | |

| (Whitford et al., 2017) | **Premise** | **Methods** | **Result** |
|------------------------|-------------|-------------|------------|
| CD dysfunction in SCZ | **Location:** California, USA | | In SCZ, CD deficit was not observed at 50 ms delay |
underlies their inability to distinguish between internally and externally generated experience

**Aim**
- To examine Investigating if corollary discharges among SCZ subjects are delayed in arriving at sensory cortex

**Sample:** SCZ=21, HC=25

**ERP Paradigm:** Participants trained to vocalize “Ah”. A sample “Ah” selected from their recording presented to them at button press at a lag of 0 ms, 50 ms and 100 ms.

**Diffusion Tensor Imaging:** 15 SCZ and 17 HC were scanned, fractional anisotropy of their arcuate fasciculus was examined for level of cortical suppression across all three conditions of the CD paradigm

condition only, out of all the three conditions. At 0 ms, N1 suppression was subnormal, at 50 ms it was supranormal and at 100 ms comparably lower than that.

- In HC unlike in SCZ, delayed stimulus delivery led to inadequate N1 suppression

- Inadequate FA of arcuate fasciculus was observed in SCZ group. Further, a linear relationship was between observed between participants’ FA in the arcuate and their pattern of N1 suppression across delay conditions

- Evidence supports disconnection hypothesis

**Implication**
- In SCZ there is a time lag in arrival of efference copy to sensory cortex causing CD. As with externally imposed delay in self-initiated stimulus delivery inadequate N1 suppression deficit looks corrected.

- Structural damage of white matter tracts in SCZ perhaps explain the conduction delays captured in ERP paradigm assessing CD.

- Aberrant physiological interactions that underlie faulty discrimination between internally and externally generated actions are perhaps mediated by WM abnormalities in fibers that connect action initiation and action reception regions of brain

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(Ford et al., 2008)

**Premise**
- Phase synchronization precedes the transmission

**Methods**
- **Location:** Chicago, USA
- **Sample:** Psychotic patients=23

**Result**
- In HC, prepress gamma band neural synchrony was maximal over the contralateral sensory-motor
of a copy of motor commands to sensory cortex, where the expected sensation (CD) is generated.

If prepress PLF (phase locking factor) reflects the activity in motor cortex, it should be contralateralized. If it reflects the action of the efference copy, it should be related to subsequent sensory suppression.

**Aim**

- To quantify the synchrony of neural events associated with the hypothesized efference copy during initiating a button press.
- To relate possible measures of the efference copy to subsequent suppression of sensory re-afference.

**ERP Paradigm:** Subjects were asked to press a button with the index finger of their right hand, at will, every 1 to 2 seconds. They were stopped after about 2 minutes of pressing or after about 50 to 60 presses. This was a control task for the talk-listen paradigm. In Talk condition, the participants made short (<300ms), sharp vocalizations of the phoneme “ah” repeatedly in a self-paced manner, about every 1–2 s, for 180 s. This speech was recorded using a microphone connected to the stimulus presentation computer and transmitted back to subjects through headphones in real time (zero delay). In listen condition, the recording from the Talk condition was played back, participants had simply listen to it.

**Prepress gamma and beta band (especially those with avolition/apathy) neural synchrony reduced in patients.**

**Implication**

- Premovement asynchrony may reflect an elemental deficit in SCZ, as observed in both prespeech and prebutton-press data. This reflects efference copy/corollary discharge mechanism dysfunction across modalities.

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**Premise**

- CD prepares the auditory cortex for incoming sound by minimizing its responsiveness and allowing the incoming sound to be tagged as self-generated.

**Methods**

- **Location:** California, USA
- **Sample:** Psychotic patients=27 (SCZ=23, SA=4); HC=26
- **ERP Paradigm:** It had four conditions –
  - **Talk condition:** Participants made short (<300ms), sharp vocalizations of
  - **Result:** N1 suppression during talking is more compared to expectancy effects based on visual warning, or simple agency effects based on self-delivery, of speech sounds.

In HC group only agency and expectancy had a modest suppression effect on N1 suppression.
**Aim**

- To explore if predictive information from expectancy (i.e., warning) and agency (i.e., self-stimulation) modulates auditory cortex in the same way and to the same degree as talking.
- To explore if these modulatory effects of expectancy and agency are deficient in SCZ in comparison to HC.

The phoneme “ah” was repeated in a self-paced manner, about every 1–2 s, for 180 s. This speech was recorded using a microphone connected to the stimulus presentation computer and transmitted back to subjects through headphones in real time (zero delay).

**Agency Condition:** Speech sounds were delivered by a self-paced button press (zero delay) and heard instantaneously. A sample of speech recorded at the beginning of the session was used as the auditory stimulus.

**Expectancy Condition:** During warned condition, a visual warning prepared subjects for the impending speech sound. A sample of speech recorded at the beginning of the session was used as the auditory stimulus, same as agency condition.

**Listen condition:** The recording from the Talk condition was played back, participants had simply listen to it.

**Implication**

- Agency and expectancy conditions do not amount to robust cortical suppression as does the talk condition. This could be because in the talk condition, “ah” sounds produced were produced in the moment and resultantly advance knowledge regarding its characteristics was close to perfect. This implies that degree of perfection regarding the knowledge of content affects N1 suppression.
- Though expectancy and agency effects may contribute to the N1 suppression seen during talking, they do not completely explain CD phenomena.
- Auditory cortical suppression effects during talking may be primarily a reflection of the specific ways motor systems are wired to send a corollary discharge of the planned actions to the specific sensory cortical areas that receive the sensory consequences of these actions.

(Judith M. Ford et al., 2007)

**Premise**

- Neural synchronization preceding self-generated actions underlie the feed forward models of actions.
- Pre-action synchrony should

**Methods**

- **Location:** California, USA
- **Sample:** SCZ=24, HC=25
- **ERP Paradigm:** Cued talk-listen paradigm - The subjects uttered “ah” while a cue (yellow X) was on the

**Result**

- Increase in phase synchrony of neural oscillations preceding speech onset in both HC and SCZ.
- Smaller prespeech neural synchrony in SCZ.
- No association between prespeech signal and N1 suppression (sign of cortical responsiveness to
be related to subsequent sensory suppression; this feature is deficient in SCZ

**Aim**

- To quantify the neural correlates of the efference copy associated with speaking, assess group differences in this neural signal and relate it to AVH

**Methods**

- **Location:** California, USA
- **Sample:** SCZ=23, HC=23
- **ERP Paradigm:** Modified talk-listen paradigm was used.
- **Talk condition:** Participants made short (<300ms), sharp vocalizations of the phoneme “ah” repeatedly in a self-paced manner, about every 1–2 s, for 180 s. This speech was recorded using a microphone connected to the screen (1.66 seconds). This was repeated five times in each of the six talk blocks. During the talk task, utterances were recorded for playback during the listen task. During the listen task, the visual display was similar to the talk task; cues were seen as before, but the instruction “TALK” was replaced with “LISTEN.”

**Result**

- In HC, N100 suppression during talk to unaltered voice feedback > N100 suppression during talk to altered voice feedback, especially over left hemisphere
- N1 suppression produced in SCZ did not show a graded pattern to altered feedback unlike HC group
- The pattern of auditory cortical responses in non-hallucinators was heterogeneous
- The strength of the N100 amplitude suppression

**Implication**

- The observed premovement burst of synchronous neural activity reflects forward model in action, preparing the CNS for the sensory consequences of self-initiated actions
- Apart from dampening irrelevant sensations resulting from our own actions, the forward model aids in differentiating between internally and externally generated percepts
- “If an efference copy of a thought or inner experience does not produce a corollary discharge of its expected sensory consequences, internal experiences may be experienced as external”.

(Heinks-Maldonado et al., 2007)

Premise

- Feed forward model posits that impressions of self-generated actions prepare sensory cortex for incoming sensation from those actions
- CD dysfunction in SCZ may contribute to the misperception of inner experiences and thoughts as AVH

Degree of prespeech synchrony in SCZ inversely correlated with auditory hallucination severity

Prespeech intertrial coherence was larger during talking than listening

Apart from dampening irrelevant sensations resulting from our own actions, the forward model aids in differentiating between internally and externally generated percepts

“If an efference copy of a thought or inner experience does not produce a corollary discharge of its expected sensory consequences, internal experiences may be experienced as external”.

“Premovement burst of synchronous neural activity reflects forward model in action, preparing the CNS for the sensory consequences of self-initiated actions”.

Cues were seen as before, but the instruction “TALK” was replaced with “LISTEN.”
Aim

- To assess the precision of the forward model in SCZ using the N1 component of the auditory event-related potential to spoken speech in real time.
- To explore the relationship between AVH and CD

Listen condition: The feedback-voice heard via headphones was varied randomly between their own unaltered voice (self, unaltered), their own voice pitch-shifted downward by 2 semitones (self, pitch-shifted), the alien unaltered voice (alien, unaltered), and the alien voice pitch-shifted downward by 2 semitones (alien, pitch-shifted).

Behavioral Response: After each trial, subjects were prompted to indicate via button press whether the feedback heard was their own voice or the alien voice or whether they were unsure. Response window was ser within 1.5 seconds after the prompt.

Implication

- Hallucinators had the smallest N1 suppression effect (to unaltered voice feedback); non-hallucinators were comparable to controls

Effect correlated with AVH severity

- Better N1 suppression to unaltered voice feedback reflects a precise forward model mechanism that enables the auditory system to distinguish between internal and external sources of auditory information
- CD in SCZ is not very precise and, instead, is more generally dysfunctional
- Heterogeneous pattern of cortical suppression in non-hallucinators may reflect differences in hallucination history, and raises the question about whether the pattern of N100 suppression reflects hallucination state or trait
- The smaller the N100 suppression effect, the more errors and the more severe the hallucinations.
- “Misattribution” is not part of the hallucinatory experience, but part of the delusional system used to explain the aberrant experience while “misperception” more accurately describes auditory hallucinations.

(Ford et al., 2002)

Premise

- Auditory cortical responsiveness is reduced during talking due to CD from frontal speech

Methods

- Location: California, USA
- Sample: SCZ=07, HC=07
- ERP Paradigm: Three equiprobable probes, each 250 m in duration, were

Result

- An interdependence between frontal and temporal areas was observed during talking in HC, this feature was somewhat disrupted in SCZ, especially those prone to auditory hallucinations.
producing areas to the speech reception areas in the temporal lobe

- Coherence is a frequency-dependent measure of the degree of relatedness between EEG recorded over two different brain areas.

**Aim**
- To assess the role of frontal speech area involvement in CD mechanism, by calculating the degree of inter-relatedness between frontal and temporal lobes during talking compared to listening, using EEG coherence algorithms.

Presented at random ISIs (0.8, 1.0 or 1.2 s): speech syllable [ba], broadband noise, and square checkerdboard. The probe sequence was presented to subjects continuously during both Listening and Talking conditions. The first prerecorded hallucinatory statement was repeated back to the subject for 30 sec (about seven repetitions). Next, the subject repeated the same statement aloud for another 30 sec. They did so silently as well in silent condition. This Listen/Talk sequence was repeated for each of the seven hallucinatory statements, for a total of 7 min.

**Analysis of Coherence**:
Data was translated data from time to frequency domain via Fast Fourier Transform (FFT) at all points. Coherence was calculated for each frequency band of interest (delta: 1–3 Hz; theta: 4–7 Hz; alpha: 8–12 Hz; beta: 13–20 Hz; gamma: 30–50 Hz). Coherence is the spectral cross-correlation between two electrodes normalized by their power spectra.

**Implication**
- The greater frontal-temporal coherence during talking than listening in HC may reflect the action of a corollary discharge from frontal brain structures preparing auditory cortex for speech.
- In HC, high levels of activation in the frontal speech areas could be related to high levels of excitation or inhibition in the temporal lobes.
- Increased coherence during talking implies a continuous dialogue between neural systems responsible for producing speech and those involved in perceiving its effects.
- N1 suppression that reflects suppression of the auditory cortex responsiveness is perhaps due to a connection between the frontal and temporal lobes that is broken or disrupted in SCZ.
- Normal effects of talking and inner speech are disrupted in SCZ.

| (Ford et al., 2001a) | **Premise** | **Methods** | **Result** |
|----------------------|------------|-------------|------------|
| ✫ CD dysfunction of auditory system in SCZ underlies | ✫ Location: California, USA | ✫ HC group produced smaller N1s to uttered than played back vowels | ✫ Sample: SCZ=07, HC=07 |
certain positive symptoms like AVH

**Aim**
- To examine CD in SCZ by ruling out the possibility of differential attention effects on N1 on speech by using ‘talk’ as the probe

**Premise**
- CD dysfunction of auditory system in SCZ mediated as failure to recognize self-generated action underlies certain positive symptoms of SCZ like AVH

**ERP Paradigm:** Talk-listen paradigm. Subjects uttered syllables [a] and [ei] for about 3 min. Each subject’s self-generated vowel sequence was recorded and played back to them through head phones, after first adjusting the gain to equalize loudnesses during playback and talking

**SCZ group did not show this reduction in N1 to their own utterances**

**Implication**
- In normal individuals a speech-related CD suppressing responsiveness of auditory cortex to self-generated speech sounds occurs
- CD mechanism of auditory cortex suppression is dysfunctional in schizophrenia

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**Methods**
- **Location:** California, USA
- **Sample:** SCZ=10, HC=12
- **ERP Paradigm:** Three equiprobable probes, each 250 m in duration, were presented at random ISIs (0.8, 1.0 or 1.2 s): speech syllable [ba], broadband noise, and square checkerboard.
- **Baseline Condition:** Subjects sat upright heard the sounds, and faced a video monitor to see the checkerboard with eyes focused on a fixation point on the screen throughout the experiment. The presentation of stimuli lasted 2 min and 42 sec.
- **Talk and listen condition:** The same sequence of probe stimuli was presented while subjects alternated between listening to their own prerecorded voice repeating a

**Result**
- Talking affected N1 to acoustic but not to visual probes
- In HC, N1 to acoustic probes was reduced during Talking compared to Baseline. In SCZ, N1 to acoustic probes was not smaller during Talking compared to Baseline.
- Baseline N1 amplitude was smaller in SCZ than in HC.
- Inner speech reduced responsiveness of auditory cortex in HC group; compared to baseline, N1 to acoustic probes was reduced when control subjects were repeating sentences silently to themselves
- Inner speech didn’t reduce auditory cortical responsiveness in SCZ

**Implication**
- N1 suppression effects are modality specific
- Corollary discharge happens automatically, without motivation or effort
hallucinatory statement (e.g., “Get off your duff and do something”) for 30 s followed by repeating that same statement for another 30 s. This alternation was repeated for seven different hallucinatory statements. This Listen/Talk sequence lasted a total of seven min.

**Inner speech and listen Condition:**
Following the presentation of probes during the silent baseline condition, self-recorded hallucinatory statements, repeated for the 30 s recording were alternated with the subjects repeating that same statement silently to themselves for 30 s. This listen/inner speech sequence was repeated seven times, once for each of seven different statements and lasted seven minutes.

As a measure of cortical responsiveness, N1 is minimally affected by attention, and these attention effects on N1 could possibly obscure our ability to detect the action of the corollary discharge.

Corollary discharge may signal speech reception areas that speech-related activations are self-generated, avoiding misperceptions that these thoughts have an external source.

SCZ – Schizophrenia / schizophrenia patients, HC – Healthy Controls, CD – Corollary discharge, ERP – Event related potential, AVH – Auditory verbal hallucination, SA – Schizo-affective patients, BPP – Bipolar disorder patients, CHR – Clinically high risk for psychosis (Individuals with attenuated Positive Symptoms, brief Intermittent Psychotic States, and/or Genetic Risk with Deterioration in social/occupational functioning); ESCZ – Early illness SCZ (individuals who fall within 2.5 years of initial hospitalization for psychosis or initiation of antipsychotic medication), FA – Fractional Anisotropy
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