Supplementary Information (SI)

Table S1.

Table S1: Mean, Standard Error, Standard Deviation, and Effect Size Data: Controls vs. Patients											
		Controls					Patients				
Measure	**Stimulation Frequency**	**Mean**	**s.e**	**s.d.**	**N**		**Mean**	**s.e.**	**s.d.**	**N**	**Effect Size**
Power	2.5 Hz	12.96	0.29	3.02	108		11.24	0.27	3.08	128	0.57
	5 Hz	13.58	0.23	2.35	108		12.39	0.28	3.20	128	0.42
	10 Hz	12.94	0.24	2.43	108		11.80	0.26	2.96	128	0.42
	20 Hz	14.60	0.23	2.36	108		14.10	0.28	3.17	128	0.18
	40 Hz	19.30	0.18	1.85	108		18.46	0.21	2.41	128	0.39
	80 Hz	16.52	0.20	2.04	108		15.55	0.37	4.20	128	0.29
PLV	2.5 Hz	0.23	0.01	0.13	108		0.18	0.01	0.12	128	0.40
	5 Hz	0.22	0.01	0.12	108		0.17	0.01	0.11	128	0.38
	10 Hz	0.21	0.01	0.11	108		0.18	0.01	0.10	128	0.32
	20 Hz	0.21	0.01	0.10	108		0.20	0.01	0.11	128	0.09
	40 Hz	0.38	0.01	0.15	108		0.33	0.01	0.16	128	0.30
	80 Hz	0.11	0.00	0.04	108		0.09	0.00	0.05	128	0.26
SI Table 2: Mean, Standard Error, Standard Deviation, and Effect Size Data: Controls vs. FDR											
		Controls					FDR				
Power	2.5 Hz	12.96	0.29	3.02	108		12.42	0.39	2.92	55	0.18
	5 Hz	13.58	0.23	2.35	108		13.50	0.39	2.86	55	0.03
	10 Hz	12.94	0.24	2.43	108		12.54	0.49	3.60	55	0.14
	20 Hz	14.60	0.23	2.36	108		13.50	0.46	3.38	55	0.40
	40 Hz	19.30	0.18	1.85	108		18.41	0.41	3.02	55	0.38
	80 Hz	16.52	0.20	2.04	108		14.80	0.74	5.49	55	0.48
PLV	2.5 Hz	0.23	0.01	0.13	108		0.19	0.02	0.12	55	0.33
	5 Hz	0.22	0.01	0.12	108		0.23	0.02	0.16	55	-0.14
	10 Hz	0.21	0.01	0.11	108		0.22	0.02	0.13	55	-0.11
	20 Hz	0.21	0.01	0.10	108		0.18	0.01	0.10	55	0.29
	40 Hz	0.38	0.01	0.15	108		0.31	0.02	0.18	55	0.39
	80 Hz	0.11	0.00	0.04	108		0.09	0.01	0.05	55	0.30

PLV: Phase locking value

FDR: First degree relatives

SI Methods:

Phase Locking Value (PLV) Computation:

PLV for each electrode at each steady state frequency rate are calculated according to the following formula

$$PLV = \frac{1}{N} \left| \sum_{k=1}^{N} e^{i\theta_k} \right|$$

where N is the number of trials and θ_k denotes the phase at the steady state frequency from the Discrete Fourier Transform. The value of PLV ranges from 0 to 1, with 1 denoting perfect phase synchrony across all trials. Increased variability of neural responses across trials reduces the PLV value and decreased variability increases the PLV value.

Description of Denoising Source Separation (DSS):

DSS is a generalized approach for optimally combining stimulus-related responses from multi-channel recordings. Simple single channel analysis ignores information available in other channels and thus wastes statistical power. Averaging responses across neighboring channels incorporates more information, but is still an *ad hoc* solution. DSS provides a systematic way of optimally combining information from every channel, each weighted according to its statistical contribution. By breaking up each EEG trial response into a fixed component (e.g., reliable with respect to the stimulus) plus random noise, the DSS procedure chooses spatial filters designed to optimally extract the reliable component. The time domain waveform of the first DSS component for each frequency is shown in **Fig. S1,** where it can be seen that DSS is able to extract ASSR responses at a high signal to noise ratio (SNR) compared to responses from a single electrode (**Fig. 2**). Channels are combined linearly with

weights chosen to optimize signal-to-noise ratio, where signal and noise can be variedly defined according to the problem in hand. We provide a short description of DSS procedure here (paraphrased from de Cheveigne et al.[37]); for a detailed description and sample applications, we refer the reader to the original article.

Consider multichannel data arranged as columns in a matrix **X** (time × channels). This multichannel data is combined linearly through an analysis matrix of weights **W** (channels × no. of components) to give DSS components **Y=XW** of dimensions time × no. of components (no. of components are less than or equal to the number of channels). Averaging over trials can reduce the noise (to enhance stimulus-evoked activity) or applying a narrow band filter can isolate the neural signal in the frequency region of interest (e.g., steady-state response). Non-averaged trials can be concatenated in time. The appropriate measure of stimulus relevance can be implemented as left-multiplication of **X** by a matrix **L**, referred to as a bias filter (where the bias favors stimulus relevance). The analysis matrix **W** can be estimated as follows,

1. Application of PCA to **X** produces a rotation matrix **P** that orthogonalizes the data, so that columns of **XP** are mutually uncorrelated in time.
2. Normalization of **XP** produces a diagonal matrix **N** that renders the data set "spherical" (unit power in all directions).
3. The bias filter **L** applied to **XPN** enhances power along the stimulus-relevant directions while reducing power in noise directions.
4. PCA applied to the filtered data **LXPN** produces a rotation matrix **Q** that aligns the relevant power with the final component axes.

The analysis matrix is obtained as **W=PNQ**, which transforms the raw observations **X** into the components **Y**, critically without the use of the bias filter **L**. The first component signal

(first column of matrix **Y**) is the linear combination with the highest possible score, according to the defined criterion of signal to noise ratio. The second component signal is uncorrelated with the first and has the next highest score, etc.. In effect, if the raw data is viewed as data in multiple dimensions, the DSS algorithm computes the optimal directions in which the signal of interest is enhanced. It should be noted that no frequency domain filtering is involved in the DSS procedure and hence is free from filtering artifacts. The bias filter used in this particular analysis is a comb-filter at the stimulus frequency and also the first four harmonics.

SI Figures:

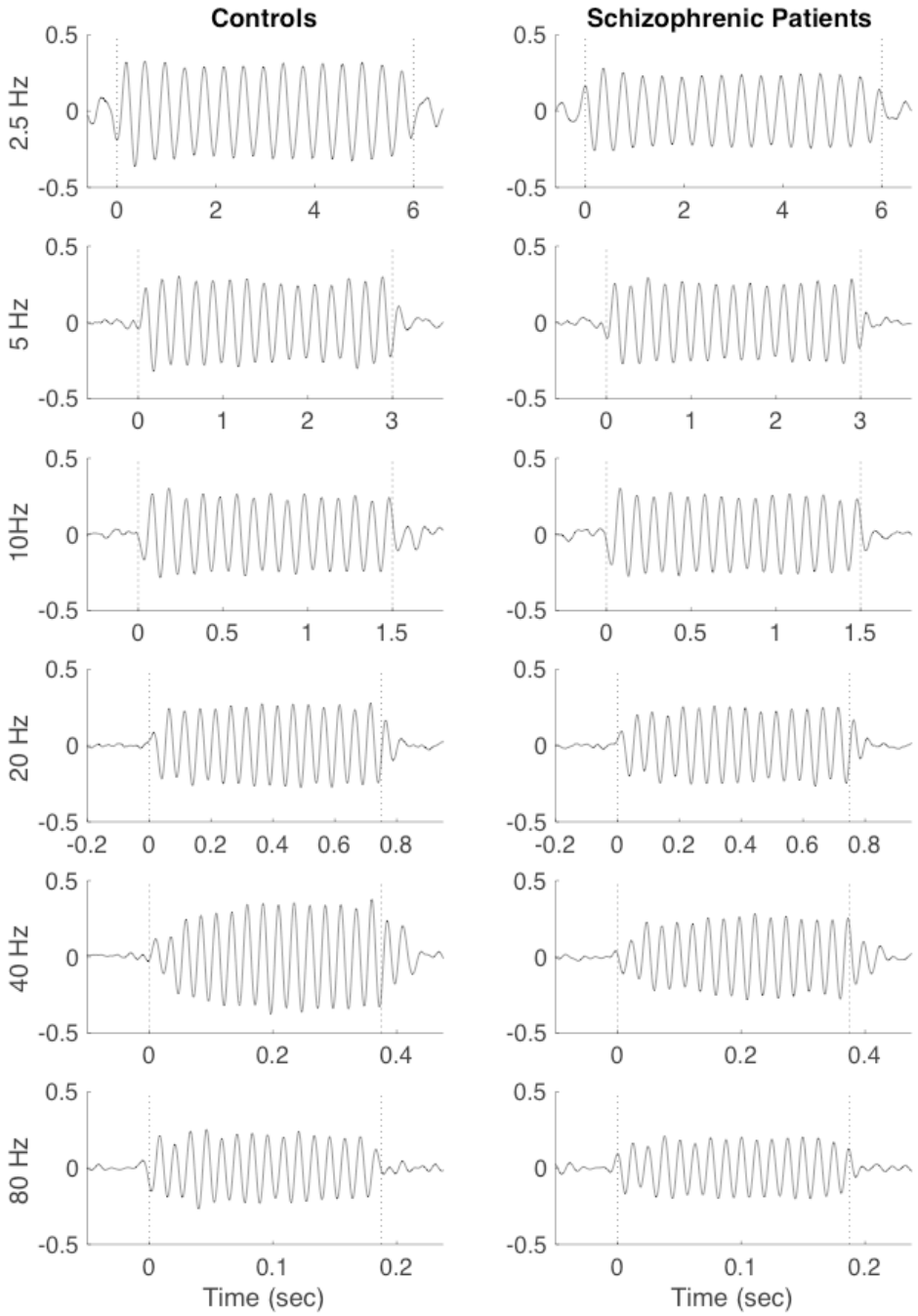

Figure S1. Time-domain grand averages using the first DSS component. DSS is able extract ASSR responses with higher SNR compared to single electrode responses (Fig 2). Note that, in controls, 2.5 Hz and 40 Hz stimuli elicit larger ASSR amplitudes than at other frequencies, and 2.5 Hz and 40 Hz stimuli are also associated with larger patient-control differences. The vertical dotted lines indicate begin and end points of a stimulus train.

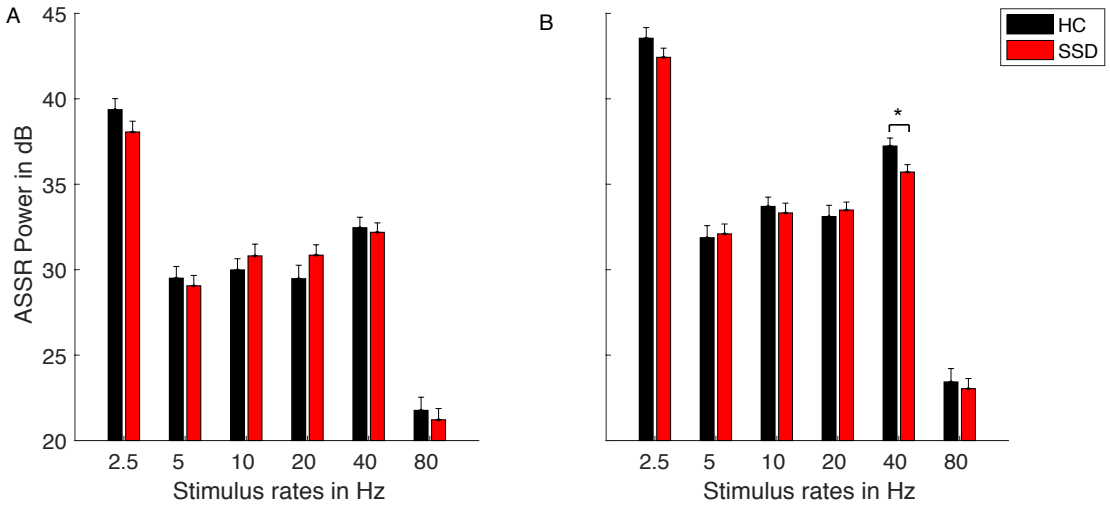

Figure S2. Mean and s.e. of absolute power at each stimulus rate based on the Discrete Fourier Transform, at recording sites CZ (A) and FZ (B), without the assistance of DSS and normalization. Even though power at 2.5 Hz is more for HC than SSD in both channels, it is not statistically significant (even without any multiple comparison correction). However, note also that, as with this non-normalized, non-DSS assisted method, ASSR responses are still the largest at 2.5 and 40 Hz. * Statistically significant without multiple comparison correction.

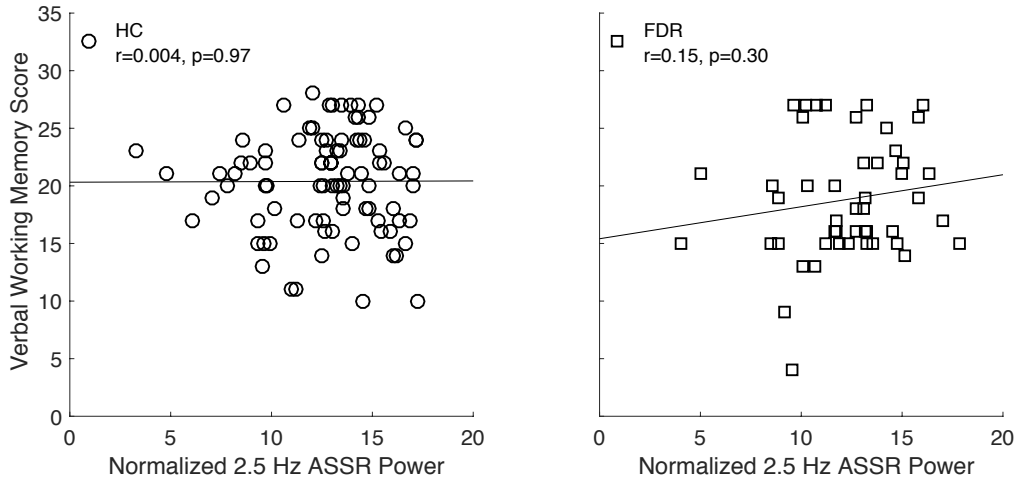

Figure S3. Association between verbal working memory and delta band ASSR in non-SSD groups. *Left*: In HC, verbal working memory showed no correlation with 2.5 Hz ASSR. *Right:* In FDR, verbal working memory showed a non-significant positive correlation with 2.5 Hz ASSR.