Developing fMRI protocol for clinical use

Comparison of 6 Arabic paradigms for brain language mapping in native Arabic speakers

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ABSTRACT

الأهداف: تقييم أساسي باستخدام ست نماذج رسم الخرائط اللغوية بالرنين المغناطيسي الوظيفي المتقدمة للناطقين بالعربية.

المنهجية: تم إجراء رسم الخرائط اللغوية بالرنين المغناطيسي الوظيفي لعدد 24 متطوع/ة الذين يستخدمون اليد اليمني اساسيا. تم استخدام جهاز رنين مغناطيسي Tesla MRI 3.0. بالنسبة إلى رسم الخرائط اللغوية بالرنين المغناطيسي الوظيفي يُستخدم BOLD لقياس الإشارات عبر الوقت عبر نماذج من 6 لغات: rhyming، وأجيال الفئات (SCG)، وتوليد الكلمات الصامتة (SWG)، وصورة توليد الفعل (VGp)، وكلمة توليد الفعل (VGw) وتوليد الفعل الصوتي (VGa). تم تحليل بيانات الرنين المغناطيسي الوظيفي باستخدام مكتبة برامج FMRIB.

النتائج: وجدنا أن VGa و SWG و VGw و VGp تم تنشيطها بقوة للمناطق المتعلقة باللغة في نصف الكرة المهيمن. فشل RH و SCG في تحديد مناطق التنشيط هذه بشكل كاف. علاوة على ذلك ، يشير التنشيط الكبير لـ IFG أثناء VGa و SWG و VGw و VGp إلى أن هذه النماذج يمكن أن تكون مثالية لتوطين منطقة Broca's في الناطقين باللغة العربية.

الخلاصة: تم وضع مجموعة من نماذج الرنين المغناطيسي الوظيفي المصادق عليها للمتحدثين باللغة العربية، مما يتيح توطين وتنسيق دقيق للغة اللغوية. يمكن استخدام هذا النوع من تقييم اللغة في التخطيط الجراحي للإجراءات الجراحية العصبية .

Objectives: To assess a baseline assessment using developed functional magnetic resonance imaging (fMRI) language paradigms for Arabic-speakers.

Methods: 24-healthy right-handed volunteers scanned on a 3.0 Tesla MRI machine. For fMRI, a BOLD-sensitive sequence used to measure signals over time across 6 language paradigms: rhyming (RH), semantic category generations (SCG), silent word generation (SWG), verb generation picture (VGp), verb generation word (VGw), and verb generation audio (VGa). fMRI data was analyzed using FMRIB Software Library (FSL).

Results: We found that VGa, SWG, VGw and VGp robustly activated language-related regions in the dominant hemisphere. RH and SCG failed to adequately define these activation regions but this may be related to the study's preliminary nature and limitations. After assessment of their validity, considerable activation of the inferior frontal gyrus during VGa, SWG, VGw and VGp suggests that these paradigms have the potential for localizing of Broca's area in native Arabic speakers.

Conclusion: Set of well adapted, and evidence-based, fMRI paradigms were established for Arabic-speakers to enable accurate and sufficient localization and lateralization of the language area. After validation, these paradigms may provide sequences for accurate localization of brain language areas, and could be used as a presurgical evaluation tool.

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Functional magnetic resonance imaging (fMRI) allows precise, and non-invasive, localization and lateralization of brain functions. Clinically, these techniques have considerable success, and hold great potential in the management of a variety of neurological disorders. One of the most promising clinical applications of fMRI is presurgical linguistic mapping.[1-5] The 3 classical language areas that are involved in language production and processing are Broca's and Wernicke's areas, and angular gyrus. Wernicke's area can be described as a receptive region, for processing and integrating auditory sensory information, while Broca's area can be described as a productive region, for making vocal signals, and meaningful words or sentences. The latter includes pars opercularis and triangularis. The angular gyrus area is particularly involved in reading and transitioning between written and spoken forms of language. Injury to language regions produces noticeable clinical deficits, and the location of these regions may become difficult to assess without advanced anatomical imaging such as fMRI. Internationally, fMRI replaces the more invasive Wada test (also known as the intracarotid sodium amobarbital procedure) in lateralizing language and memory at some centers.[6,7]

Language is a highly complex system that markedly varies across individuals. Patients native language affects brain activation responses during fMRI scans.[8-13] As such, language paradigms for presurgical fMRI mapping should be developed and validated using native language paradigms. Language dominance of the left cerebral hemisphere has been well researched and established, but native language and social factors were also reported to play a key role in cortical association of verbal processing.[8,14-16]

Although language localization using fMRI has been routinely used in western countries, and more recently in an Arabic country,[17] studies clearly demonstrated that different cultures may process language in different manners, using different brain mechanisms.[8,14-16] Existing language paradigms, created for non-Arabic speaking patients, require major modifications before applying them in examining native Arabic speakers.[17]

Language lateralization is another broadly used clinical application of fMRI. Concordance with Wada test has long been demonstrated and validated in the literature using paradigms with various tasks such as verbal fluency, comprehension, and semantic judgment .[18-21] These have shown that concordance with Wada test can reach 90% in temporal lobe epilepsy, especially in left-dominant patients. A slightly lower concordance was achieved in right-dominant patients. Although fMRI language lateralization works well for patients with typical language dominance, clinicians need to be careful when interpreting results of patients with atypical language representation.[22]

Semitic languages such as Arabic differ from other languages in many aspects, including orthography (including diacritics), phonology, and syntax. Therefore, significant research in developing and validating language paradigms for Arabic is required. To our knowledge, very few studies in this domain have been carried out.[17,23] One developed several language and memory paradigms in neurological patients, while emphasizing consideration for educational and cultural adjustments,[17] and the other examined neuronal correlates of diacritics (vs. lack of thereof) in 11 healthy men.[23]

We aim to establish tasks adapted to the Arabic language, that also reliably activate Broca's and Wernicke's areas in a relatively short scanning time. This study is a baseline assessment using 6 developed fMRI language paradigms for Arabic-speaking presurgical candidates. The desired outcome of this work is to create a set of Arabic language localization protocols, along with standard operating procedures.

Methods.

Participants. This prospective pilot study was done at King Faisal Specialist Hospital & research center (KFSH&RC). Ethical approval was obtained from the institutional review board of KFSH&RC. The study was conducted in accordance with the Helsinki Declaration. Radiological data were kept strictly confidential. Literature review was performed through electronic search (Google Scholar, PubMed). The purpose of the study was explained to participants in both oral and written forms, and informed consent was obtained. Twenty-four healthy adults (50% men) age 22 to 39 years (mean=29.41 years) participated in this study. Each participant was asked to fill a form relating to MRI room safety. Exclusion criteria included presence of known neurological or psychiatric diseases, pregnancy, visual or hearing defects, or any brain pathology or abnormal brain morphology. Participants were all right-handed native Arabic speakers. Handedness has been measured using the Edinburgh Handedness Inventory (mean laterality index was 0.86).[24]

Task. Based on a review of commonly used fMRI designs in neurolinguistic studies,[25-28] we developed 8 paradigms to investigate the neural basis brain regions of different language aspects such as syntactic, semantic, and phonologic processing. Our tasks aimed on assessing language areas in the frontal and temporal lobes. Two of the developed tasks (Sentence Completion and Object Naming) were not used in data collection (one because of challenges relating to collection of response accuracy, and the latter due to being covered by other tasks as to region activation). The remaining 6 paradigms had the

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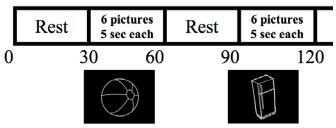
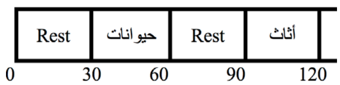
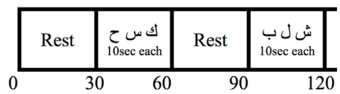
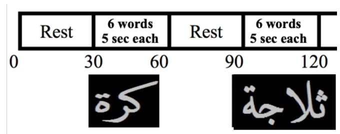
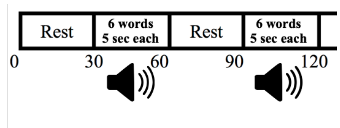
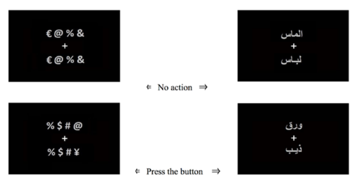
same scanning duration time, which is 4:30 minutes, except rhyming (6:48 minutes). Block design was used with action and rest length of 30 seconds each, except rhyming. Each paradigm had four activation onsets and five resting intervals (apart from rhyming, described below), starting and finishing the paradigm with a resting moment. In all paradigms (apart from rhyming), during the rest block, a crosshair was presented to the subjects, and they were asked "to-do-nothing" at rest while keeping eyes open (**Table 1**).

Paradigms detail. 1. Rhyming (RH). This paradigm is aimed to activate language areas in the left dorsolateral prefrontal cortex (DLPC), Broca's area and the posterior lateral fusiform gyrus, supramarginal gyrus, and superior temporal gyrus, and is largely based on method used by Lurito and his colleagues.[26] Nonetheless, Arabic word rhymes did not yield the same variety in task complexity as the original English task by this group: That is, words written in Arabic ending with the same spelling had much higher chances of rhyming, whereas in English words could be spelled similarly at the end, but do not rhyme ("comb" and "tomb"). This may have landed the task relatively easier to complete than the English format. Words were selected from a pool of high

Table 1 - Summary of all 6 tasks; Picture Verb Generation (VGp), Semantic Category Generations (SCG), Silent Word Generation (SWG), Verb Generation words (VGw), Verb Generation audio (VGa), and Rhyming (RH).

#	Task	Task description	Duration	Images
1	VGp	• Alternating 4-ON/5-OFF blocks with 30 s per block. • In each ON block; 6 black/white images were presented. • Participant was asked to think of as much as he/she can of (action words) from each image that showed during the scan. And to relax when the crosshair appeared on the screen, with his/her eyes kept open.	270 sec	
2	SCG	• Alternating 4-ON/5-OFF blocks with 30 s per block. • It consisted of different categories displayed during ON blocks. • The participant was asked to think as much as he/she can about names in the same category displayed (animals, furniture, fruit & vegetable, cloths).	270 sec	
3	SWG	• Alternating 4-ON/5-OFF blocks with 30 s per block. • Three Arabic letters were displayed in each ON block • Participant was asked to think about words starting with the letter displayed, and to do nothing at rest with keeping his/her eyes open.	270 sec	
4	VGw	• Alternating 4-ON/5-OFF blocks with 30 s per block. • In each ON block; six nouns were presented. • Participant instructed to think of a verb that is associated with the noun that showed during the scan. For example, the word "ball" might generate the verb "hit". And to relax when the crosshair appeared on the screen, with his/her eyes kept open.	270 sec	
5	VGa	• It is similar to VGw, although stimuli were presented in different order through the headphones. • Patients were instructed to think of the response, but not to vocalize it.	270 sec	
6	RH	• This paradigm started and ended with 12 sec rest moment. • Consisted of 16 blocks, 8 blocks of pair words and 8 blocks of pair symbols interleaved to each other. • Total of 64 pairs of word and 64 pairs of symbols, where pairs remained for 3 sec. • Participant was asked to press the button on the response pad when non-rhyme.	408 sec	

VGp - Verb Generation - Picture Format, SCG - Semantic Category Generations, SWG - Silent Word Generation, VGw - Verb Generation words, VGa - Verb Generation audio, RH - rhyming, sec - second

Table 2 - Lateralization of brain activity has been assessed for each participant by calculating the laterality index (LI) across these region of interest (ROI).

IFG (POP)	Inferior Frontal Gyrus (Pars Opercularis)
IFG (PTR)	Inferior Frontal Gyrus (Pars Triangularis)
AG	Angular Gyrus
SMG	Supramarginal Gyrus
MTG	Middle Temporal Gyrus
STG	Superior Temporal Gyrus

frequency words, and reviewed by a Native Arabic clinical neuropsychologist and an Arabic language teacher. Attention was made to select words with high frequency (based on dictionary by Buckwalter[29], and concreteness and familiarity (qualitatively). Imaginability aspects were not addressed. The task started and ended with 12-second rest moment. It consisted of 16 blocks, eight blocks of pair words, and eight blocks of pair symbols, interleaved to each other. Each block contained eight different pairs of word or symbol pairs (total of 64 pairs of word and 64 pairs of symbols) that remained for three seconds, and was displayed to the participant through goggles. Participants were asked to press a button on the response pad when stimuli do not-rhyme (**Table 1**). Nonetheless, participants responses were not collected during neither format of rhyming, and activation data was collected for the word rhymes only. There were efforts or providing auditory instructions and formats of the tasks (e.g. verb generation as presented in auditory format vs. written word format) in an attempt to have some of these paradigms available for illiterate or low educated people in the future.

2. Semantic Category Generations (SCG). This paradigm is a single word semantic word fluency task, based on method by Kircher et el.[25] Semantic fluency has been associated with activation in the temporal (fusiform gyrus) and left middle frontal lobes.[30] It consisted of four different semantic categories, presented in the form of a word display for 30 seconds, followed by rest blocks of 30 seconds, and repeated over the whole scan which lasted for 4:30 minutes. Categories included animals, furniture, fruit and vegetables, and clothes. The participant was asked to think about words belonging to the category displayed (**Table 1**).

3. Silent Word Generation (SWG). As an attempt to assess activation in the DLPC and inferior frontal

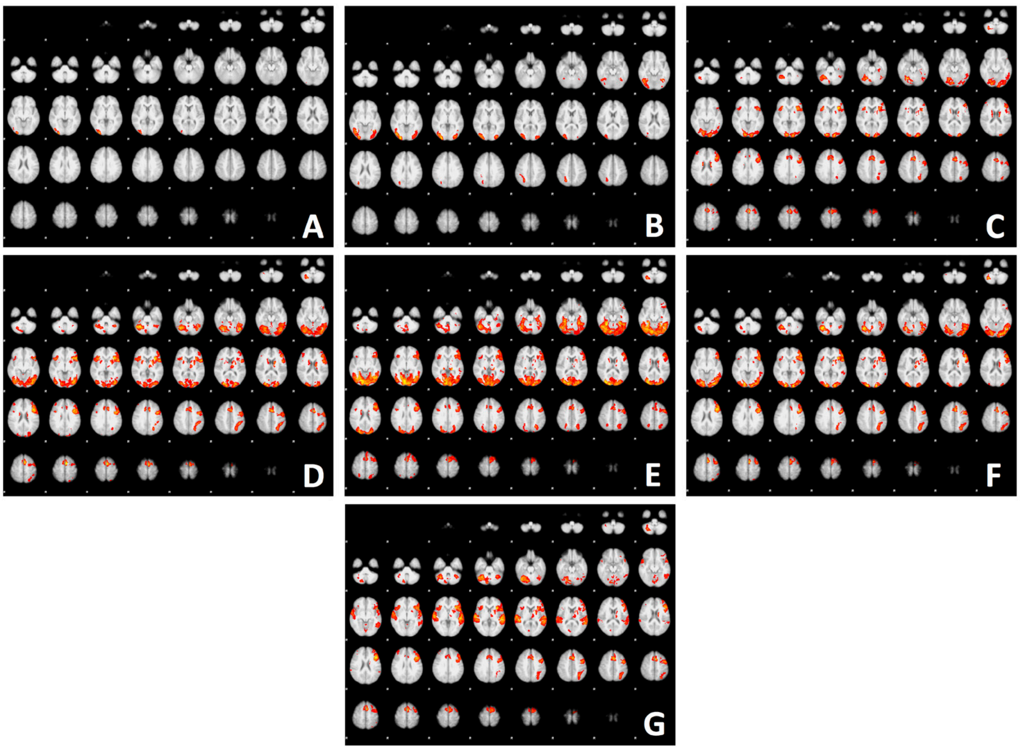


Figure 1 - Statistical grand average map of fMRI response to **A**) Words Rhyme (RH), **B**) Symbols Rhyme (RH), **C**) Semantic Category Generation (SCG) task, **D**) Silent Word Generation (SWG) task, **E**) Picture Verb Generation (VGp) task, to **F**) Verb Generation words (VGw) task, **G**) Verb Generation audio (VGa) task overlaid on 36 axial slices of the MNI152_T1_2mm standard image included in FSL. The (Red-yellow) color shows fMRI signal level (Z-scores) above the 0.05 significance threshold.

Table 3 - Details of activated cerebral areas in 24 volunteers (mean values) during the Verb Generation audio (VGa) task.

Cluster Index	Voxels	*P*	$-\log_{10}(P)$	Z MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	Region Name
1	13898	0.000	80.5	7.3	-44	18	26	L Inferior Frontal Gyrus (pars opercularis)
				6.68	-66	-18	10	L Superior Temporal Gyrus
				6.65	-34	20	2	L Insular Cortex
				6.45	-44	26	22	L Inferior Frontal Gyrus (pars triangularis)
2	3116	0.000	28.8	6.54	-2	14	48	L Paracingulate Gyrus
				6.11	-4	6	58	L Supplementary Motor Cortex
				5.94	2	20	48	R Paracingulate Gyrus
				5.62	-10	4	64	L Superior Frontal Gyrus
				5.57	-12	14	38	L Paracingulate Gyrus
3	1777	0.000	19.3	6.32	62	-14	6	R Planum Temporale
				5.29	40	22	-2	R Frontal Operculum Cortex
				5.21	62	4	-2	R Superior Temporal Gyrus
				5.19	64	-8	4	R Planum Temporale
				4.9	30	28	4	R Frontal Orbital Cortex
				4.87	60	4	-10	R Superior Temporal Gyrus
4	967	0.000	12.4	5.87	-28	-66	48	L Lateral Occipital cortex (superior division)
				5.64	-32	-58	44	L Superior Parietal Lobule
				4.92	-40	-50	48	
				4.29	-30	-74	42	L Lateral Occipital Cortex
				4.28	-32	-70	40	
				4.05	-30	-46	40	L Superior Parietal Lobule
5	317	0.000	5.13	4.68	-28	-22	-2	L Left Putamen
				4.6	-10	-28	-6	Brain-Stem
6	180	0.001	3.06	3.81	18	4	16	R Caudate
				3.74	18	10	4	R Putamen
				3.57	18	12	16	R Caudate
7	170	0.001	2.89	4.34	46	44	30	R Frontal Pole
				4.06	38	50	30	
				3.83	42	36	30	
				3.75	38	36	22	
8	137	0.005	2.31	4.13	2	-60	-12	Cerebellum (R V)
				4.04	-2	-54	-14	Cerebellum (L I-IV)
				3.96	2	-52	-6	Cerebellum (R I-IV)
				3.76	0	-50	-14	Cerebellum (L I-IV)
				3.31	-8	-52	-14	Cerebellum (L V)
9	121	0.010	2.01	4.07	8	-24	-12	Brain-Stem
				3.81	6	-30	-4	
				3.43	10	-32	-6	
10	89	0.043	1.37	3.63	14	-78	14	R Intracalcarine Cortex
				3.52	10	-80	10	

gyrus, this covert word generation task,[25,26,28] three Arabic letters were displayed in each block (each letter lasted for 10 seconds), followed by 30 seconds rest, alternating over 4:30 minutes. Participants were asked to think about words starting with the displayed letter, and to do nothing at rest, while keeping eyes open (**Table 1**). Letter were selected based on a Saudi study exploring difficulty in generating words for each of the Arabic alphabet[31] They were presented in the order of difficulty, with letters generating more words (based on the study), were placed earlier. This was proposed to increase participants' task engagement. Covert format

Table 4 - Details of activated cerebral areas in 24 volunteers (mean values) during the Silent Word Generation (SWG) task.

Cluster Index	Voxels	*P*	$-\log_{10}(P)$	Z MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	Region Names
1	13118	0.000	81.8	6.57	-44	-68	-20	L Occipital Fusiform Gyrus
				6.4	-40	-78	-2	L Lateral Occipital Cortex
				6.33	26	-88	14	R Lateral Occipital Cortex
2	8645	0.000	61.6	7.05	-4	4	60	L Supplementary Motor Cortex
				6.72	-44	20	24	L Inferior Frontal Gyrus (pars opercularis)
				6.63	-32	20	2	L Insular Cortex
				6.52	-8	18	34	L Cingulate Gyrus
				6.28	-2	14	48	L Para-Cingulate Gyrus
				6.18	-28	24	2	L Insular Cortex
3	1519	0.000	18.4	6.16	-40	-42	46	L Superior Parietal Lobule
				5.33	-28	-64	36	L Lateral Occipital Cortex
				5.32	-28	-64	50	
				5.2	-28	-56	50	L Superior Parietal Lobule
				4.98	-26	-60	44	L Lateral Occipital Cortex
				4.95	-34	-44	38	L Supramarginal Gyrus
4	845	0.000	12	5.72	34	18	2	R Insular cortex
				5.49	30	28	0	R Frontal Orbital Cortex
				5	46	20	-4	R Frontal Operculum Cortex
				4.86	52	16	2	R Inferior Frontal Gyrus (pars opercularis)
				4.74	40	28	2	R Frontal Operculum Cortex
				4.3	46	18	8	R Inferior Frontal Gyrus (pars opercularis)
5	382	0.000	6.53	5.14	22	8	6	R Putamen
				4.29	16	-2	22	R Caudate
				4.23	18	10	18	
				4.15	26	4	0	R Putamen
				4.13	12	6	8	R Caudate
6	242	0.000	4.43	4.49	44	32	18	R Middle Frontal Gyrus
				4	42	38	22	R Frontal Pole
				3.89	42	40	34	
				3.55	40	48	28	
7	224	0.000	4.14	3.98	2	-52	-12	Cerebellum (R I-IV)
				3.89	2	-46	-8	
				3.84	8	-40	-22	
				3.83	2	-40	-20	
				3.83	-2	-48	-20	Cerebellum (L I-IV)
8	108	0.009	2.01	4.69	42	12	28	R Inferior Frontal Gyrus (pars opercularis)
9	98	0.016	1.8	3.47	34	-28	-26	Temporal Fusiform Cortex

was chosen since data was not collected on response accuracy.

4. Verb Generation - Picture Format (VGp). Verb generation tasks have been associated with activation in the inferior frontal gyrus (IFG).[32,33] In this task, there were six black/white images in each activation block and each single line image lasting for 5 seconds. The total was 24 different images.

Participants were asked to think of as many verbs (action words) they could as prompted by each image shown during the scan. They were asked to relax when the crosshair screen appeared, while eyes kept open (**Table 1**). The pictures used were derived from database by Songrass and Vanderwart[34] as well as drawings from a local database. The set of verb prompting stmilui were finalized by a clinical psychologist based on word frequency, as well as familiarity (qualitatively).

5. Verb Generation words (VGw). Here, same set

Table 5 - Details of activated cerebral areas in 24 volunteers (mean values) during the Verb Generation words (VGw) task.

Cluster Index	Voxels	*P*	$-\log_{10}(P)$	Z MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	Region Name
1	7813	0.000	57.7	6.27	-42	18	24	L Inferior Frontal Gyrus (pars opercularis)
				6.1	-50	20	26	
				6.04	-6	6	58	L Supplementary Motor Cortex
				5.73	-44	8	26	L Inferior Frontal Gyrus (pars opercularis)
				5.72	-2	16	48	L Para-cingulate Gyrus
				5.67	-50	18	16	L Inferior Frontal Gyrus (pars opercularis)
2	5527	0.000	45.6	6.37	34	-60	-26	Cerebellum (R VI)
				6.21	40	-64	-28	Cerebellum (R Crus)
				6.12	18	-96	0	R Occipital Pole
				6.08	20	-98	8	
				6.04	16	-86	-6	R Lingual Gyrus
				5.99	26	-96	8	R Occipital Pole
3	5172	0.000	43.5	6.29	-18	-94	6	L Occipital Pole
				6.14	-16	-98	0	
				6.14	-16	-100	8	
				6.02	-50	-66	-12	L Lateral Occipital Cortex
				5.97	-18	-90	-12	L Occipital Fusiform Gyrus
				5.94	-34	-36	-24	L Temporal Fusiform Cortex
4	1318	0.000	16.7	5	-30	-48	38	L Supramarginal Gyrus (posterior division)
				4.88	-28	-70	52	L Lateral Occipital Cortex
				4.87	-26	-60	44	
				4.82	-28	-64	48	
				4.72	-34	-56	46	L Superior Parietal Lobule
				4.66	-24	-66	44	L Lateral Occipital Cortex
5	257	0.000	4.69	4.36	40	18	4	R Frontal Operculum Cortex
				4.29	30	24	4	R Insular Cortex
				3.67	46	18	10	R Inferior Frontal Gyrus (pars opercularis)
				3.28	36	32	-2	R Frontal Orbital Cortex

of stimuli as in the VGp tasks were , but in a different order, and using prompts in a single-written word form. A noun was projected onto a screen, and participants were instructed to think of a verb that was associated with it. For example, the word "ball" might generate the verb "hit" (**Table 1**).

6. Verb Generation audio (VGa). In this task, the same set of words as the VGw task above were used, but with the words presented auditory through headphones. As the other two VG tasks, participants were instructed to think of responses, but not to vocalize it (**Table 1**).

Stimulus Presentation. Stimuli were presented using Nordic Neurolabs (NNL) (Bergen, Norway) head-coil mounted goggles and electrostatic headphones.

Data acquisition and analysis. Imaging acquisitions were performed on a 3.0 Tesla MRI scanner (TRIO SIEMENS) at the imaging facilities of KFSH&RC. A high-resolution anatomical scan was obtained over four minutes. For fMRI, BOLD-sensitive sequences were used to measure the signal over time across a variety of language localization paradigms. Functional volumes were collected every three ms, echo time of 30 ms, matrix size of 64X64, and flip angel of 90o. Slices were selected for each subject based on anatomical landmarks, and the functional tasks employed. Functional scans were conducted to examine six different stimulation paradigms per subjects. The total scanning time was approximately 33 minutes (1988 seconds).

FMRIB Software Library (FSL) software was used to analyze fMRI data. Functional data were preprocessed to remove low frequency linear drift in the signal from in each functional data set. Motion correction, temporal filtering, and spatial smoothing (5mm FWHM Gaussian window) of the data were applied to increase the signal to noise ratio. For this aspect of data preprocessing, standard filtering techniques available in

Table 6 - Details of activated cerebral areas in 24 volunteers (mean values) during the Picture Verb Generation (VGp) task.

Cluster Index	Voxels	*P*	$-\log_{10}(P)$	Z MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	Region Name
1	24524	0.000	111	7.02	8	-84	-4	R Lingual Gyrus
				6.98	16	-96	14	R Occipital Pole
				6.96	8	-90	-4	
				6.79	12	-82	-10	R Lingual Gyrus
				6.77	30	-52	-18	R Temporal Occipital Fusiform Cortex
				6.66	-14	-100	8	R Occipital Pole
2	7798	0.000	50.9	6.11	-46	20	26	L Middle Frontal Gyrus
				5.39	-2	14	48	L Para-Cingulate Gyrus
				5.31	-30	28	4	L Insular Cortex
				5.27	-42	10	28	L Inferior Frontal Gyrus (pars opercularis)
				5.25	-38	26	-4	L Frontal Orbital Cortex
3	351	0.000	5.3	4.98	30	28	-2	R Frontal Orbital Cortex
				4.72	36	20	0	R Insular Cortex
				4.02	40	28	-6	R Frontal Orbital Cortex
				3.84	44	16	0	R Frontal Operculum Cortex
				3.22	48	26	0	R Inferior Frontal Gyrus (pars triangularis)
4	317	0.000	4.86	4.86	-18	0	18	L Caudate
				4.22	-18	12	12	
				4.18	-18	8	6	L Putamen
				4.08	-14	10	8	L Caudate
5	162	0.002	2.64	6.43	-22	-30	0	L Thalamus
				5.02	-6	-30	-2	Brain-Stem
				3.78	-16	-32	-8	L Para-hippocampal Gyrus
6	159	0.003	2.59	4.62	40	6	30	R Precentral Gyrus
7	145	0.004	2.36	4.31	18	2	18	R Caudate
				4.08	18	12	18	
				3.72	20	12	6	R Putamen
8	90	0.043	1.37	5.81	22	-28	2	R Thalamus
				5.54	24	-28	8	

FSL were applied. Individual activation maps from each patient were obtained. The size of the activated area was calculated from the volume of activation exceeding a significance threshold of $p<0.001$ and forming a cluster significance of $p<0.05$. Activation peaks and size of areas of activation were directly correlated with participants' anatomical MRI. Participants had the opportunity to learn and practice the task before running the fMRI experiment. A board-certified neuroradiologist screened all images and no abnormalities were detected in any participant.

Laterality index. Lateralization of brain activity has been assessed for each participant by calculating the laterality index (LI). It was calculated as the proportion of active voxels in the left versus the right region of interest (ROI) (**Table 2**) averaged across multiple thresholds.[35] Using the cluster tool in FSL, we test the effects of different thresholds on the second-level whole brain map by setting a threshold, and a range of z-values at (z=1.0, z=1.5, z=2.3). Then the total numbers of active voxels in all ROIs in both hemispheres were determined by using the Fslstats tool. Finally, we used the formula: LI = (left–right) / (left+right) to calculate LI. This yields a score for LI range from +1 (all left hemisphere activation only) to −1 (all right hemisphere activation only) and the intermediate values reflect varying degrees

Table 7 - Details of activated cerebral areas in 24 volunteers (mean values) during the Semantic Category Generation (SCG) task.

Cluster Index	Voxels	*P*	-log$_{10}$(*P*)	Z MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	Region Name
1	6583	0.000	45	6.73	18	-94	4	R Occipital Pole
				6.01	-16	-98	12	
				5.91	-14	-98	2	L Occipital Pole
				5.75	-16	-98	6	
2	3513	0.000	29.2	6.43	-34	24	4	L Frontal Operculum Cortex
				5.86	-18	-8	22	L Caudate
				5.48	-40	20	24	
				5.42	-46	22	24	L Middle Frontal Gyrus
				5.3	-46	18	28	
				5.16	-48	38	16	L Frontal Pole
3	2602	0.000	23.6	5.83	-4	14	48	L Para-Cingulate Gyrus
				5.8	-6	6	60	L Supplementary Motor Cortex
				5.69	-2	4	60	
				5.23	-2	22	44	L Para-Cingulate Gyrus
				5.23	4	8	60	R Supplementary Motor Cortex
				5.13	4	4	62	
9	511	0.000	7.22	4.93	-26	-62	44	
				4.13	-28	-70	44	L Lateral Occipital cortex (superior division)
				4.04	-28	-70	52	
5	468	0.000	6.62	5.28	32	20	2	R Insular cortex
				4.97	30	28	0	R Frontal Orbital Cortex
6	216	0.000	3.45	4.8	18	6	18	
				4.79	18	-2	24	R Caudate
				4.7	18	-8	24	
				3.61	24	6	6	R Putamen
7	181	0.001	2.92	4.02	42	48	24	R Frontal Pole
				3.64	48	48	20	

of laterality.[35] This method was most appropriate for this study as tasks differed in the type of software used.

Results. Group activation maps of 24 subjects for the six Arabic language paradigms; RH, SCG, SWG, VGp, VGw and VGa are shown in (**Figures 1 A-G**). As shown in the figures, robust activation of the recognized language areas are shown in all paradigms, except in RH and SCG, which were ineffective to activate these language regions.

Four of our fMRI paradigms were successful at activating the well-known language regions (Broca's and Wernicke's areas). Amongst all of the six language paradigms, VGa presented the best localization of the language functions. VGa paradigm revealed the strongest activation (largest volume and highest signal change) in the inferior frontal gyrus (IFG) particularly pars opercularis (POP) and para triangularis (PTR), and the superior temporal gyrus (STG) (**Figure 1 G, Table 3**). SWG paradigm demonstrated the second strongest activation in IFG (POP) and supramarginal gyrus (SMG) (**Figure 1-E, Table 4**). The third strongest activation was in the VGw paradigm was also in IFG (POP) and SMG (**Figure 1-D, Table 4**). VGp paradigm showed the fourth strongest activation, which also activate the IFG (POP) (**Figure 1-E, Table 5**). Rh and SCG paradigm did not display any activation in the Broca's or Wernick's area (**Figure 1-A, B & C, Table 6**). As mentioned earlier that a negative value signify right-hemisphere dominance, while positive LI scores value signify left-hemisphere dominance. Left hemisphere dominant/lateralized patterns of activation were confirmed among our participants in this study (**Figure 1**).

For the SWG task, LI values were as follows: IFG (POP) (LI=0.56±0.16), IFG (PTR) (LI=0.45±0.18), AG (LI=0.47±0.34), SMG (LI=0.53±0.28), MTG (LI=0.33±0.37), and STG (LI=0.36±0.28). For the VGa task, LI values were as follows: IFG (POP) (LI= 0.53±0.23), IFG (PTR) (LI=0.41±0.29), AG

(LI=0.35±0.31), SMG (LI=0.29±0.28), MTG (LI=0.07±0.25), and STG (LI=0.11±0.21). For the VGw task, LI values were as follows: IFG (POP) (LI=0.64±0.18), IFG (PTR) (LI=0.57±0.22), AG (LI=0.59±0.25), SMG (LI=0.59±0.25), MTG (LI= 0.54±0.27), and STG (LI=056±0.23). For the VGp task, LI values were as follows: IFG (POP) (LI=0.53±0.14), IFG (PTR) (LI=0.49±0.17), AG (LI=0.55±0.33), SMG (LI=0.47±0.43), MTG (LI=0.47±0.29), and STG (LI=0.45±0.36).

Discussion. In the context of scarce literature of Arabic language fMRI protocols, this study makes available 6 novel, and culturally adapted, Arabic language paradigms, with the aim of serving, via language mapping, a neurosurgical population. We also found that most of our paradigms was able to activate known language-related areas, as well as determine hemispheric dominance in all subjects. The VGa, SWG, VGw and VGp were found to be the most robust paradigms.

Results of VGa, SWG, VGw and VGp are consistent with other studies.[36,37] Additionally, activation of IFG during the VGa, SWG, VGw and VGp suggests that these paradigms model localization of well-known language regions (Broca's area) in native Arabic speakers.

The results of this study also showed that VGw was the strongest paradigm for language lateralization in the ROIs of the dominant language hemisphere, followed in sequences by VGp, SWG, and VGa.

In contrast, RH and SCG showed bilateral activation patterns leading to unsuccessful language lateralization. Compared to other four paradigms, they activated large pattern of other cortical regions that are not essential for language production, involving the imagery pathway and more sub-processes of language production. This does not implicate that they are not suitable for clinical examination, but may suggest that they are in need of further investigation, after eliminating some study limitations.

The highest LIs and activations of the classical anterior language areas in VGa, SWG, VGw and VGp can be due to the nature of these tasks. Activations detected in Wernicke's area during VGa, SWG, VGw, and VGp might make these paradigms essential models of language tasks for Arabic patients. They show promising utility once validity studies and clinical are completed. Further, studies are warranted to use them while examining different factors such as age, education, handedness, and multilinguality may affect.[14-17,38] Brain plasticity and organization of function is another area worthy of examining using these protocols.[39,40]

One limitation of this study is the lack of comparison with active baseline tasks. Through removing unwanted visual-related activation, active baselines might have increased robustness of our findings, and helped increase tool validity. The SCG and RH data might be best reassessed with this approach in further studies. Not including illiterate subjects or real patients in the study is another limitation. Our next step is to apply these paradigms in comparison with the standard of Wada test to validate the newly developed tools. Another limitation is reverting to covert responses, and not collecting data on response accuracy. Since this study was preliminary, emphasis was placed on experimenting with the newly developed designs, and less on methods of exploring correspondence between activation and accuracy. This, nevertheless, remains a main goal for future studies of our tools' validity.

In conclusion, six paradigms, developed based on neuropsychological evidence, are now made available for further clinical examination, and potential to replace invasive presurgical tests for native Arabic speakers.

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